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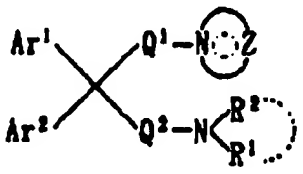
(54) Title: DIPHENYLMETHANE DERIVATIVES AS MIP-1α/RANTES RECEPTOR ANTAGONISTS

(57) Abstract

An MIP-1α/RANTES-receptor antagonist which comprises the compound of formula (I), wherein Ar^1 and Ar^2 independently represent an optionally substituted aromatic group; Q^1 and Q^2 independently represent an optionally substituted divalent C_{1-6} aliphatic hydrocarbon group which may have either oxygen or sulfur within the carbon chain; R^1 represents hydrogen atom, an optionally substituted lower alkyl group or an optionally substituted lower alkyl-carbonyl group; R^2 represents an optionally substituted hydrocarbon group or an optionally substituted acyl group, or R^1 and R^2, taken together with the adjacent nitrogen atom, form an optionally substituted nitrogen containing heterocyclic group; and a group of formula (a) represents an optionally substituted nitrogen-containing mono or fused heterocyclic group, or a salt thereof.



[I]

(a)

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DESCRIPTION

DIPHENYLMETHANE DERIVATIVES AS MIP-1ALPHA/RANTES RECEPTOR ANTAGONISTS

TECHNICAL FIELD

This invention relates to a compound which has a MIP-1α/RANTES receptor antagonism and is useful for preventing or treating allergic diseases (e.g. bronchial asthma, atopic dermaritis, etc.), inflammatory diseases (e.g. arteriosclerosis, rheumatoid arthritis, etc.) and multiple sclerosis.

BACKGROUND ART

Chemokines are a group of cytokines regulating chemotaxis of leukocytes and it has recently been becoming clear that chemokines and other cytokines have relevance to the progression and exacerbation of conditions of diseases in the acute and chronic periods of inflammatories.

It is known that, among chemokines, RANTES (regulated on activation, normal T expressed and secreted) and MIP-1α (macrophage inflammatory protein-1α) belong to CC chemokines and act on lymphocytes, monocytes, eosinophils and basophils to enhance migration and further show a direct leucocyte activation, e.g. degranulation, secretion of various inflammatory mediator, etc. (Clinical Immunotherapy Vol. 4, pages 1-8, 1995).

Particularly, an increase in amount of gene expression of RANTES is observed in synovia of rheumatism patients (Clinical & Experimental Immunology, Vol. 101, page 398, 1995; and Lancet, Vol. 343, page 547, 1994) or focus of arteriosclerosis, which suggests that they are concerned with the diseases. It has also beem reported that in administration of a MIP-1α antibody to mice delays crisis of arthritis and ameliorates the symptoms (The Journal of American Soci ty for Clinical Investigation,

Vol. 95, page 2868, 1995). However, antibodies are macromolecules and have a problem about oral absorption and stability.

MIP-1α/RANTES receptor described in this specification means a mutual receptor among chemokines, for example, MIP-1α, RANTES or MCP-3 (monocyte chemoattractant protein-3), etc., which is called CCR1 (Nature Medicine, page 1174, 1996).

According to the above background, it has been desired to develop a novel drug as a CCR1 receptor antagonist/agonist. Although a peptide antagonist for a RANTES receptor is known (Journal of Biological Chemistry, 27, 18, page 12521-10527(1996)), it has a problem about oral absorption and stability.

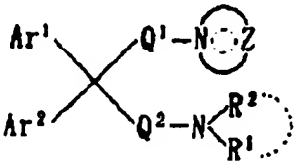
It has been becoming apparent that eosinophils and basophils are concerned in recruitment, progression and exacerbation of various allergic diseases and inflammatory diseases due to aggregation to the inflammatory site and activation. Therefore, It is considered that immunopathy diseases (e.g. bronchial asthma, atopic dermatis, arteriosclerosis, articular rheumatism, etc.) may be prevented or treated by inhibiting the action of the above chemokines (Clinical Immunotherapy Vol. 4, pages 1-8, 1995). However, such antagonists have never been reported so far.

On the other hand, a lot of diphenylmethane derivatives have hitherto been synthesized (Journal of Medicinal Chemistry, Vol. 34, page 12, 1991; Arch. int. Pharmacodyn., Vol. 107, page 194, 1956; Japanese Patent Kokai (Laid-Open) No. 123164/1987). For example, loperamide is commercially available as antidiarrheic. It is also known that loperamide has a calmodulin antagonism but it is not known that it inhibits migration of cells induced by the chemokines. It is not known that haloperidol having a 4-hydroxypiperidyl group used as an antipsychotic agent has the action.

It has been desired to develop a MIP-1α/RANTES receptor antagonist and a novel drug inhibiting diseases caused by RANTES or MIP-1α.

DISCLOSURE OF INVENTION

The inventors of this invention have intensively studied. As a result, it has been found that a compound of the formula:



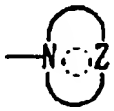
[I]

wherein Ar^1 and Ar^2 independently represent an optionally substituted aromatic group;

Q^1 and Q^2 independently represent an optionally substituted divalent C_{1-6} aliphatic hydrocarbon group which may have oxygen or sulfur within the carbon chain;

R^1 is a hydrogen atom, an optionally substituted lower alkyl group or an optionally substituted lower alkyl-carbonyl group;

R^2 is an optionally substituted hydrocarbon group or an acyl group, or R^1 and R^2, taken together with the adjacent nitrogen atom, may form an optionally substituted nitrogen-containing heterocyclic ring; and a group of the formula:



is an optionally substituted monocyclic or fused nitrogen-containing heterocyclic group, or a salt thereof has an excellent MIP-1α/RANTES receptor antagonism, unexpectedly, on the basis of a specific chemical structure of the formula:

This invention has been accomplished on the basis of the above discovery.

This invention is, therefore, directed to:

(1) A MIP-1α/RANTES receptor antagonist comprising a compound [I] or a salt thereof,

(2) A composition as described in the above item (1), wherein

Ar^1 and Ar^2 independently represent (A) a monocyclic or fused polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms, or (B) a 5- to 11-membered monocyclic or fused heteroaromatic group having at least one of 1 or 2 kinds of hetero atoms selected from nitrogen, sulfur and oxygen in addition to carbon atoms, said heterocyclic group being optionally fused with the monocyclic or fused polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms, each of which may have a substituent selected from the group consisting of

(I) a halogen atom,

(II) a C_{1-3} alkylenedioxy group,

(III) a nitro group,

(IV) a cyano group,

(V) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(VI) a C_{2-6} alkenyl group optionally having 1 to 3 halogen atoms,

(VII) a C_{2-6} alkynyl group optionally having 1 to 3 halogen atoms,

(VIII) a C_{3-6} cycloalkyl group,

(IX) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms,

(X) a C_{1-6} alkylthio group optionally having 1 to 3 halog n atoms,
(XI) a hydroxyl group,
(XII) an amino group,
(XIII) a mono-C_{1-6} alkylamino group,
(XIV) a di-C_{1-6} alkylamino group,
(XV) a 5- to 7-membered cyclic amino group,
(XVI) an acylamino group which is shown by the formula:
(i) $-NHCOOR^3$, (ii) $-NHCONHR^3$, (iii) $-NHCOR^3$ or (iv) $-NHSO_2R^3$ wherein R^3 is (1) a C_{1-6} alkyl group, (2) a C_{2-6} alkenyl group, (3) a C_{2-6} alkynyl group, (4) a C_{3-6} cycloalkyl group which may be fused with a benzene ring optionally having 1 to 3 C_{1-6} alkoxy groups, (5) a C_{6-10} aryl group or (6) a C_{7-16} aralkyl group, each of a group shown by above items (1) to (6) optionally having 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(XVII) a C_{1-6} alkyl-carbonyl group,
(XVIII) a carboxyl group,
(XIX) a C_{1-6} alkoxy-carbonyl group,
(XX) a carbamoyl group,
(XXI) a mono-C_{1-6} alkyl-carbamoyl group,
(XXII) a di-C_{1-6} alkyl-carbamoyl group,
(XXIII) a C_{6-10} aryl-carbamoyl group,
(XXIV) a sulfo group,
(XXV) a C_{1-6} alkylsulfonyl group,
(XXVI) a C_{6-10} aryl group, and
(XXVII) a C_{6-10} aryloxy group;

Q^1 and Q^2 independently represent
(I) a C_{1-6} alkylene group,
(II) a C_{2-6} alkenylene group, or
(III) a C_{2-6} alkynylene group, each of a group shown by the above items (I) to (III) may have oxygen or optionally oxydized sulfur within the carbon chain;

R^1 is
(I) a hydrogen atom,
(II) a C_{1-6} alkyl group which may have 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl gr up, (v) a C_{6-10} aryl

group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, or

(III) a C_{1-6} alkyl-carbonyl group which may have 1 to 5 substituents selected from (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally or fused with a benzene ring;

R^2 is

(I) a C_{1-6} alkyl group,

(II) a C_{2-6} alkenyl group,

(III) a C_{2-6} alkynyl group,

(IV) a C_{3-6} cycloalkyl group which may be fused with a benzene ring optionally having 1 to 3 C_{1-6} alkoxy groups,

(V) a C_{6-10} aryl group,

(VI) a C_{7-16} aralkyl group,

each of a group shown by above the items (1) to (6)

optionally having 1 to 5 substitu nts selected from the group consisting of (a) a halog n atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, or

(VII) an acyl group which is shown by the formula: $-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$, $-(C=O)O-R^4$, $-(C=S)O-R^4$, or $-(C=S)NR^5R^4$, wherein R^4 is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{2-6} alkenyl group,

(iv) a C_{2-6} alkynyl group,

(v) a C_{3-6} cycloalkyl group which may be fused with a benzene ring optionally having 1 to 3 C_{1-6} alkoxy groups,

(vi) a C_{6-10} aryl group,

(vii) a C_{7-16} aralkyl group,

(viii) a 5- to 11-membered heterocyclic group having at least one hetero atom s lected from nitrogen, oxyg n and sulfur in addition to carbon atoms, said

heterocyclic group being optionally fused with a benzene ring,
(ix) a C_{1-6} alkyl-carbonyl group,
(x) a carboxyl group,
(xi) a C_{1-6} alkoxy-carbonyl group,
(xii) a mono-C_{1-6} alkyl-carbamoyl group,
(xiii) a di-C_{1-6} alkyl-carbamoyl group,
(xiv) a 5- to 7-membered cyclic amino group, or
(xv) a C_{6-10} aryloxy group,
each of a group shown by the above items (ii) to (xv) optionally having 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally substituted with (e-1) a halogen atom, (e-2) a C_{1-3} alkylenedioxy group, (e-3) a nitro group, (e-4) a cyano group, (e-5) a C_{3-6} cycloalkyl group, (e-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (e-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (e-8) a hydroxyl group, (e-9) an amino group, (e-10) a mono-C_{1-6} alkylamino group, (e-11) a di-C_{1-6} alkylamino group, (e-12) a C_{1-6} alkyl-carbonyl group, (e-13) a carboxyl group, (e-14) a C_{1-6} alkoxy-carbonyl group, (e-15) a carbamoyl group, (e-16) a mono-C_{1-6} alkyl-carbamoyl group, (e-17) a di-C_{1-6} alkyl-carbamoyl group, (e-18) a C_{6-10} aryl-carbamoyl group, (e-19) a sulfo group, (e-20) a C_{1-6} alkylsulfonyl group, (e-21) a C_{6-10} aryl group, (e-22) a C_{6-10} aryloxy group or (e-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group

optionally having 1 to 3 halog n atoms, (i) a C_{7-16} aralkyl group, (j) a hydroxyl group, (k) an amino group which may be substituted with a C_{1-6} alkyl carbonyl group, (l) a mono-C_{1-6} alkylamino group, (m) a di-C_{1-6} alkylamino group, (n) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (n-1) a halogen atom, (n-2) a C_{1-3} alkylenedioxy group, (n-3) a nitro group, (n-4) a cyano group, (n-5) a C_{3-6} cycloalkyl group, (n-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (n-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (n-8) a hydroxyl group, (n-9) an amino group, (n-10) a mono-C_{1-6} alkylamino group, (n-11) a di-C_{1-6} alkylamino group, (n-12) a C_{1-6} alkyl-carbonyl group, (n-13) a carboxyl group, (n-14) a C_{1-6} alkoxy-carbonyl group, (n-15) a carbamoyl group, (n-16) a mono-C_{1-6} alkyl-carbamoyl group, (n-17) a di-C_{1-6} alkyl-carbamoyl group, (n-18) a C_{6-10} aryl-carbamoyl group, (n-19) a sulfo group, (n-20) a C_{1-6} alkylsulfonyl group, (n-21) a C_{6-10} aryl group, (n-22) a C_{6-10} aryloxy group or (n-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (o) a carboxyl group, (p) a C_{1-6} alkoxy-carbonyl group, (q) a formyl group which may be substituted with 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfure in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (r) a carbamoyl group, (s) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (s-1) a halogen atom, (s-2) a C_{1-3} alkylenedioxy group, (s-3) a nitro group, (s-4) a cyano group, (s-5) a C_{3-6} cycloalkyl group, (s-6) a C_{1-6} alkoxy group optionally having 1 to 3 halog n at ms, (s-7) a

C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (s-8) a hydroxyl group, (s-9) an amino group, (s-10) a mono-C_{1-6} alkylamino group, (s-11) a di-C_{1-6} alkylamino group, (s-12) a C_{1-6} alkyl-carbonyl group, (s-13) a carboxyl group, (s-14) a C_{1-6} alkoxy-carbonyl group, (s-15) a carbamoyl group, (s-16) a mono-C_{1-6} alkyl-carbamoyl group, (s-17) a di-C_{1-6} alkyl-carbamoyl group, (s-18) a C_{6-10} aryl-carbamoyl group, (s-19) a sulfo group, (s-20) a C_{1-6} alkylsulfonyl group, (s-21) a C_{6-10} aryl group, (s-22) a C_{6-10} aryloxy group or (s-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (t) a di-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (t-1) a halogen atom, (t-2) a C_{1-3} alkylenedioxy group, (t-3) a nitro group, (t-4) a cyano group, (t-5) a C_{3-6} cycloalkyl group, (t-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (t-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (t-8) a hydroxyl group, (t-9) an amino group, (t-10) a mono-C_{1-6} alkylamino group, (t-11) a di-C_{1-6} alkylamino group, (t-12) a C_{1-6} alkyl-carbonyl group, (t-13) a carboxyl group, (t-14) a C_{1-6} alkoxy-carbonyl group, (t-15) a carbamoyl group, (t-16) a mono-C_{1-6} alkyl-carbamoyl group, (t-17) a di-C_{1-6} alkyl-carbamoyl group, (t-18) a C_{6-10} aryl-carbamoyl group, (t-19) a sulfo group, (t-20) a C_{1-6} alkylsulfonyl group, (t-21) a C_{6-10} aryl group, (t-22) a C_{6-10} aryloxy group or (t-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (u) an optionally halogenated C_{6-10} aryl-carbamoyl group, (v)

an optionally halogenated C_{6-10} aryl-carbonyl group, (w) a sulfo group which may be substitut d with an amino group, (x) a C_{1-6} alkylsulfonyl group, (y) a C_{6-10} aryl group, (z) a C_{6-10} aryloxy group, (aa) a C_{2-6} alkenylamino group, (bb) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (cc) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (dd) a C_{1-6} alkoxy-carbamoyl group, (ee) a carbamoyloxy group, (ff) a sulfamoyl group, (gg) a mono-C_{1-6} alkyl-sulfamoyl group, and (hh) a di-C_{1-6} alkyl-sulfamoyl group;

R^5 is

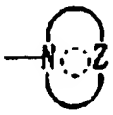
(I) a hydrogen atom or

(II) a C_{1-6} alkyl group;

or R^1 and R^2, taken together with the adjacent nitrogen atom, form a 4- to 8-membered heterocyclic group optionally having at least one nitrogen and 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, which may have 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group,

(r) a di-C_{1-6} alkyl-carbamoyl gr up, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, and (w) a C_{6-10} aryloxy group;

a group of the formula:



is (1) a 4- to 9-membered monocyclic ring or (2) 6- to 14-membered bicyclic ring, each of which may have 1 or 2 unsaturated bonds and optionally having 1 or 2 substituents selected from the group consisting of

(i) a C_{1-6} alkyl group,

(ii) a C_{1-6} alkoxy group,

(iii) a C_{1-6} alkylthio group, each of a group shown by the above items (i) to (iii) may have 1 to 5 substituents selected from (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkyl-carbamoyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(iv) a hydroxyl group,
(v) an amino group,
(vi) a mono-C_{1-6} alkylamino group,
(vii) a di-C_{1-6} alkylamino group,
(viii) a C_{1-6} alkyl-carbonyl group,
(ix) a carboxyl group,
(x) a C_{1-6} alkoxy-carbonyl group,
(xi) a carbamoyl group,
(xii) a mono-C_{1-6} alkyl-carbamoyl group,
(xiii) a di-C_{1-6} alkyl-carbamoyl group,
(xiv) a C_{6-10} aryl-carbamoyl group,
(xv) a sulfo group,
(xvi) a C_{1-6} alkylsulfonyl group,
(xv) a C_{6-10} aryl group, and
(xvi) a C_{6-10} aryloxy group,

(3) A composition as described in the above item (1) wherein R^1 is a hydrogen atom or a C_{1-6} alkyl group,

(4) A composition as described in the above item (1) wherein R^1 is a hydrogen atom or methyl,

(5) A composition as described in the above item (1) wherein R^1 is a hydrogen atom,

(6) A composition as described in the above item (1) wherein R^2 is an acyl group,

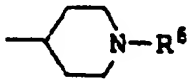
(7) A composition as described in the above item (6) wherein the acyl group is of the formula $-(C=O)-R^4$, $-SO_2-R^4$, $-SO-R^4$, $-(C=O)NR^5R^4$, $-(C=O)O-R^4$, $-(C=S)O-R^4$, or $-(C=S)NR^5-R^4$,
wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxy-carbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group, an optionally

substituted 5- or 7-membered cyclic amino group or an optionally substituted aryloxy group; and R^5 is a hydrogen atom or a lower alkyl group,

(8) A composition as described in the above item (6), wherein the acyl group is of the formula $-(C=O)-R^4$ or $-(C=O)NHR^4$, wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxy-carbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group, an optionally substituted 5- or 7-membered cyclic amino group or an optionally substituted aryloxy group; and R^5 is a hydrogen atom or a lower alkyl group,

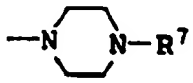
(9) A composition as described in the above item (8), wherein R^4 is a group of the formula:

(A)



or

(B)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with

(b-1) a halogen atom, (b-2) a C_{1-3} alkylenedioxy group, (b-3) a nitro group, (b-4) a cyano group, (b-5) a C_{3-6} cycloalkyl group, (b-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (b-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (b-8) a hydroxyl group, (b-9) an amino group, (b-10) a mono-C_{1-6}

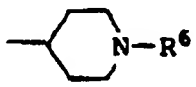
alkylamino group, (b-11) a di-C_{1-6} alkylamino group, (b-12) a C_{1-6} alkyl-carbonyl group, (b-13) a carboxyl group, (b-14) a C_{1-6} alkoxy-carbonyl group, (b-15) a carbamoyl group, (b-16) a mono-C_{1-6} alkyl-carbamoyl group, (b-17) a di-C_{1-6} alkyl-carbamoyl group, (b-18) a C_{6-10} aryl-carbamoyl group, (b-19) a sulfo group, (b-20) a C_{1-6} alkylsulfonyl group, (b-21) a C_{6-10} aryl group, (b-22) a C_{6-10} aryloxy group or (b-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{3-6} cycloalkyl group, (d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (e) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (f) a C_{7-16} aralkyl group, (g) a hydroxyl group, (h) an amino group, (i) a mono-C_{1-6} alkylamino group, (j) a di-C_{1-6} alkylamino group, (k) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (k-1) a halogen atom, (k-2) a C_{1-3} alkylenedioxy group, (k-3) a nitro group, (k-4) a cyano group, (k-5) a C_{3-6} cycloalkyl group, (k-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (k-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (k-8) a hydroxyl group, (k-9) an amino group, (k-10) a mono-C_{1-6} alkylamino group, (k-11) a di-C_{1-6} alkylamino group, (k-12) a C_{1-6} alkyl-carbonyl group, (k-13) a carboxyl group, (k-14) a C_{1-6} alkoxy-carbonyl group, (k-15) a carbamoyl group, (k-16) a mono-C_{1-6} alkyl-carbamoyl group, (k-17) a di-C_{1-6} alkyl-carbamoyl group, (k-18) a C_{6-10} aryl-carbamoyl group, (k-19) a sulfo group, (k-20) a C_{1-6} alkylsulfonyl group, or (k-21) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said

heterocyclic group being optionally fus d with a b nz ne ring, (l) a carboxyl group, (m) a C_{1-6} alkoxy-carbonyl group, (n) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (o) a carbamoyl group, (p) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (p-1) a halogen atom, (p-2) a C_{1-3} alkylenedioxy group, (p-3) a nitro group, (t-4) a cyano group, (p-5) a C_{3-6} cycloalkyl group, (p-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (p-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (p-8) a hydroxyl group, (p-9) an amino group, (p-10) a mono-C_{1-6} alkylamino group, (p-11) a di-C_{1-6} alkylamino group, (p-12) a C_{1-6} alkyl-carbonyl group, (p-13) a carboxyl group, (p-14) a C_{1-6} alkoxy-carbonyl group, (p-15) a carbamoyl group, (p-16) a mono-C_{1-6} alkyl-carbamoyl group, (p-17) a di-C_{1-6} alkyl-carbamoyl group, (p-18) a C_{6-10} aryl-carbamoyl group, (p-19) a sulfo group, (p-20) a C_{1-6} alkylsulfonyl group, (p-21) a C_{6-10} aryl group, (p-22) a C_{6-10} aryloxy group or (p-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (q) a di-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (q-1) a halogen atom, (q-2) a C_{1-3} alkylenedioxy group, (q-3) a nitro group, (q-4) a cyano group, (q-5) a C_{3-6} cycloalkyl group, (q-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (q-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (q-8) a hydroxyl group, (q-9) an amino group, (q-10) a mono-C_{1-6} alkylamino group, (q-11) a di-C_{1-6}

alkylamino group, (q-12) a C_{1-6} alkyl-carbonyl group, (q-13) a carboxyl group, (q-14) a C_{1-6} alkoxy-carbonyl group, (q-15) a carbamoyl group, (q-16) a mono-C_{1-6} alkyl-carbamoyl group, (q-17) a di-C_{1-6} alkyl-carbamoyl group, (q-18) a C_{6-10} aryl-carbamoyl group, (q-19) a sulfo group, (q-20) a C_{1-6} alkylsulfonyl group, (q-21) a C_{6-10} aryl group, (q-22) a C_{6-10} aryloxy group or (q-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (r) an optionally halogenated C_{6-10} aryl-carbamoyl group, (s) an optionally halogenated C_{6-10} aryl-carbonyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group, (x) a C_{2-6} alkenylamino group or (y) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

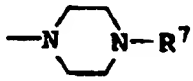
(10) A composition as described in the above item (8), wherein R^4 is a group of the formula:

(A)



or

(B)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with

(b-1) a hydroxyl group, (b-2) a di-C_{1-6} alkylamino group, (b-3) a C_{1-6} alkoxy-carbonyl group, or (b-4) a 5-

to 7-membered heterocyclic group having 1 to 3 hetero atoms select d from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{7-16} aralkyl group, (d) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (d-1) a halogen atom, (d-2) a mono-C_{1-6} alkylamino group, (d-3) a C_{1-6} alkoxy-carbonyl group, or (d-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (e) a C_{1-6} alkoxy-carbonyl group, (f) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (g) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (g-1) a halogen atom, or (g-2) a C_{1-6} alkyl-carbonyl group, (h) an optionally halogenated C_{6-10} aryl-carbamoyl group, (i) an optionally halogenated C_{6-10} aryl-carbonyl group, or (j) a C_{6-10} aryloxy group,

(11) A composition as described in the above item (1) wherein Q^1 and Q^2 are independently a C_{1-6} alkylene group which may have an oxo group,

(12) A composition as described in the above item (1) wherein Q^1 is a C_{1-4} alkylene group and Q^2 is a methylene group,

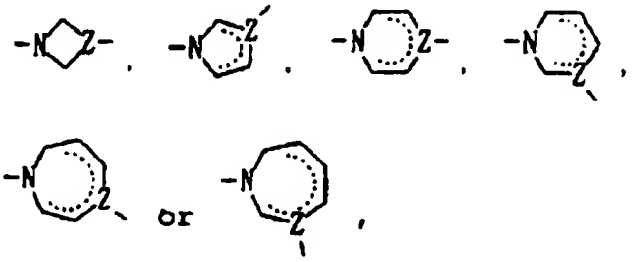
(13) A composition as described in the above item (1) wherein the ring of the formula:

is a 4- to 9-membered mon cyclic ring or 6- to 14-

member d bicyclic ring, which may have 1 or 2 unsaturated bonds and may hav 1 or 2 substituents in any position other than N and Z,

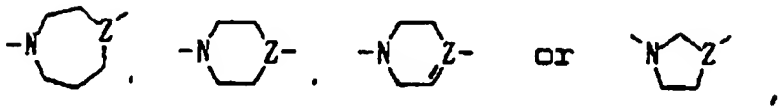
(14) A composition as described in the above item (1) wherein the ring of the formula:

is



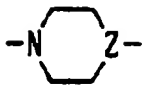
(15) A composition as described in the above item (1) wherein the ring of the formula:

is



(16) A composition as described in the above item (1) wherein the ring of the formula:

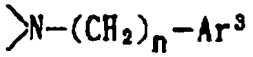
is



(17) A composition as described in the above item (13) wherein Z is

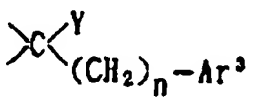
(A) an optionally substituted 1, 2-phenylene,

(B) a group of the formula:



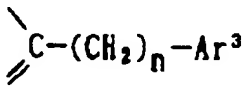
wherein Ar^3 is an optionally substituted aromatic group, and n is an integer of 0 to 3,

(C) a group of the formula:



wherein Ar^3 and n have the same meanings as defined above; and Y is (i) a hydrogen atom, (ii) an optionally halogenated lower alkyl group, (iii) an optionally halogenated lower alkoxy group, (iv) an optionally halogenated lower alkylthio group, (v) a hydroxyl group, (vi) a cyano group, (vii) an alkyl-carbonyl group, (viii) a lower alkyl-carbonyloxy group, (ix) a formylamino group, (x) an amino group, (xi) a mono-lower alklylamino group, (xii) a di-lower alkylamino group, (xiii) a carboxyl group, (xiv) a lower alkoxy-carbonyl group or (xv) a lower alkyl-carbonylamino group, or

(D) a group of the formula:



wherein Ar^3 and n have the same meanings as defined above, or

(E) a group of the formula:

$$>C=CH-(CH_2)_n-Ar^3$$

wherein Ar^3 and n have the same meanings as defined above,

(18) A composition as described in the above item (1) wherein the ring of the formula:

is pyrrolidine, piperidine, piperazine, azepine or azocine, each of which may be fused with a benzene ring and may have a substituent,

(19) A composition as described in the above item (13) wherein Z is a group of the formula:

$$>C<^{Y}_{(CH_2)_n-Ar^3}$$

wherein Ar^3 is an optionally substituted aromatic group, n is an integer of 0 to 3, and Y is a hydrogen atom or a hydroxyl group,

(20) A composition as described in the above item (19) wherein Ar^3 is a C_{6-14} aryl group or a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, each of which may have 1 to 3 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl group, and an optionally halogenated C_{1-6} alkoxy group,

(21) A composition as described in the above item (19) wherein Ar^3 is a phenyl group optionally substituted with a halogen atom,

(22) A composition as described in th abov item (19) wherein n is 0,

(23) A composition as described in the above item (19) wherein Y is a hydroxyl group,

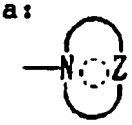
(24) A composition as described in the above item (1) wherein Ar^1 and Ar^2 independently represent a C_{6-14} aryl group or a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, each of which may have 1 to 3 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl group, and an optionally halogenated C_{1-6} alkoxy group,

(25) A composition as described in the above item (1) wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl,

(26) A composition as described in the above item (1), wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

Q^1 is a C_{1-4} alkylene group; Q^2 is a methylene group;

the group of the formula:



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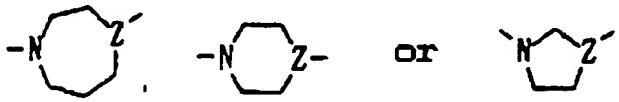
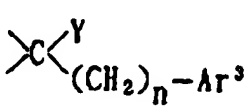


wherein Z is a group of the formula:



wherein Ar^3 is a phenyl group optionally substituted with a halogen atom, n is an integer of 0 to 3, and Y is a hydrogen atom or a hydroxyl group;

R^1 is a hydrogen atom or methyl;

R^2 is (I) an C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group or a formyl group or (II) an acyl group represented by the formula:

$-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)OR^4$

wherein R^4 is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group which may have 1 to 5 substituents selected from (a) a hydroxyl group, (b) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (c) a mono-C_{1-6} alkylamino group, (d) a di-C_{1-6} alkylamino group, (e) a carboxyl group, (f) a C_{1-6} alkoxy-carbonyl group, (g) a mono-C_{1-6} alkyl-carbamoyl group, (h) a sulfo group which may be substituted with amino group, (i) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (j) a C_{1-6} alkoxy-carbamoyl group, and (k) a carbamoyloxy group,

(iii) a C_{2-6} alkenyl group,

(iv) a C_{6-10} aryl group,

(v) a 5- to 11-membered heterocyclic group having at least one hetero atom selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,

(vi) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkyl-carbonyl group,

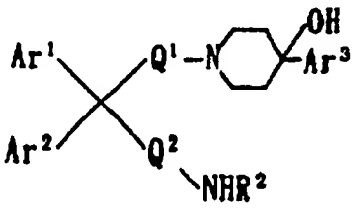
(vii) a carboxyl group which may be substituted with a C_{1-6} alkyl group,

(viii) a 5- to 7-membered cyclic amino group which may be substituted with

(a) a C_{1-6} alkyl group optionally substituted with (a-1) a hydroxyl group, (a-2) a di-C_{1-6} alkylamino group, (a-3) a C_{1-6} alkoxy-carbonyl group or (a-4) a 5- to 7-membered heter cyclic group having 1 to 3 hetero atoms

selected from nitrogen, oxygen and sulfur in addition to carbon or fused with benzene ring,
(b) a C_{7-16} aralkyl group, (c) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (c-1) a halogen atom, (c-2) a mono-C_{1-6} alkylamino group, (c-3) a C_{1-6} alkoxy-carbonyl group or (c-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,
(d) a C_{1-6} alkoxy-carbonyl group, (e) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to a carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(f) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with a halogen atom or a C_{1-6} alkyl-carbonyl group, (g) an optionally halogenated C_{6-10} aryl-carbamoyl group, (h) an optionally halogenated C_{6-10} aryl carbonyl group or (i) a C_{1-6} alkoxy-carbamoyl group, or
(ix) a C_{6-10} aryloxy group; and
R^5 is a hydrogen atom or a C_{1-6} alkyl group,

(27) A compound of the formula:



[II]

wherein Ar^1, Ar^2 and Ar^3 independently represent an optionally substituted aromatic group;

Q^1 and Q^2 independently represent a divalent C_{1-6} aliphatic hydrocarbon group, which may have oxygen or

sulfur within the carbon chain; and

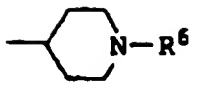
R^2 is an optionally substituted hydrocarbon group or an acyl group or a salt thereof (except N-[5-[4-(4-chlorophenyl-4-hydroxypiperidino-2,2-diphenylpentyl]-1-methanesulfonamide hydrochloride, N-[5-[4-chlorophenyl)-4-hydroxypiperidino-2,2-diphenylpentyl]-1-(p-toluene)sulfonamide hydrochloride and N-[5-(4-(4-chlorophenyl)-4-hydroxypiperidino-2,2-diphenylpentyl]-1-(2-thiophene)sulfonamide hydrochloride),

(28) The compound as described in the above item (27) wherein R^2 is a group of the formula $-(C=O)-R^4$, $-(C=O)NR^5R^4$, $-(C=O)O-R^4$, $-(C=S)O-R^4$ or $-(C=S)NR^5R^4$ wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxylcarbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group or an optionally substituted 5- or 7-membered cyclic amino group; and R^5 is a hydrogen atom or a lower alkyl group,

(29) A compound as described in the above item (27), wherein R^2 is the formula $-(C=O)-R^4$ or $-(C=O)NH-R^4$, wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxylcarbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group or an optionally substituted 5- or 7-membered cyclic amino group,

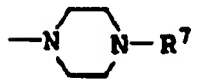
(30) A compound as described in the above item (28), wherein R^4 is of th formula:

(A)



or

(B)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with (b-1) a halogen atom, (b-2) a C_{1-3} alkylenedioxy group, (b-3) a nitro group, (b-4) a cyano group, (b-5) a C_{3-6} cycloalkyl group, (b-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (b-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (b-8) a hydroxyl group, (b-9) an amino group, (b-10) a mono-C_{1-6} alkylamino group, (b-11) a di-C_{1-6} alkylamino group, (b-12) a C_{1-6} alkyl-carbonyl group, (b-13) a carboxyl group, (b-14) a C_{1-6} alkoxy-carbonyl group, (b-15) a carbamoyl group, (b-16) a mono-C_{1-6} alkyl-carbamoyl group, (b-17) a di-C_{1-6} alkyl-carbamoyl group, (b-18) a C_{6-10} aryl-carbamoyl group, (b-19) a sulfo group, (b-20) a C_{1-6} alkylsulfonyl group, (b-21) a C_{6-10} aryl group, (b-22) a C_{6-10} aryloxy group or (b-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{3-6} cycloalkyl group, (d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (e) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (f) a C_{7-16} aralkyl group, (g) a hydroxyl group, (h) an amino group, (i) a mono-C_{1-6} alkylamino group, (j) a di-C_{1-6} alkylamino group, (k) a C_{1-6} alkyl-carbonyl group whose

alkyl portion may be substituted with (k-1) a halogen atom, (k-2) a C_{1-3} alkylenedioxy group, (k-3) a nitro group, (k-4) a cyano group, (k-5) a C_{3-6} cycloalkyl group, (k-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (k-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (k-8) a hydroxyl group, (k-9) an amino group, (k-10) a mono-C_{1-6} alkylamino group, (k-11) a di-C_{1-6} alkylamino group, (k-12) a C_{1-6} alkyl-carbonyl group, (k-13) a carboxyl group, (k-14) a C_{1-6} alkoxy-carbonyl group, (k-15) a carbamoyl group, (k-16) a mono-C_{1-6} alkyl-carbamoyl group, (k-17) a di-C_{1-6} alkyl-carbamoyl group, (k-18) a C_{6-10} aryl-carbamoyl group, (k-19) a sulfo group, (k-20) a C_{1-6} alkylsulfonyl group, or (k-21) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (l) a carboxyl group, (m) a C_{1-6} alkoxy-carbonyl group, (n) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (o) a carbamoyl group, (p) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (p-1) a halogen atom, (p-2) a C_{1-3} alkylenedioxy group, (p-3) a nitro group, (t-4) a cyano group, (p-5) a C_{3-6} cycloalkyl group, (p-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (p-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (p-8) a hydroxyl group, (p-9) an amino group, (p-10) a mono-C_{1-6} alkylamino group, (p-11) a di-C_{1-6} alkylamino group, (p-12) a C_{1-6} alkyl-carbonyl group, (p-13) a carboxyl group, (p-14) a C_{1-6} alkoxy-carbonyl group, (p-15) a carbamoyl group, (p-16) a mono-C_{1-6}

alkyl-carbamoyl group, (p-17) a di-C_{1-6} alkyl-carbamoyl group, (p-18) a C_{6-10} aryl-carbamoyl group, (p-19) a sulfo group, (p-20) a C_{1-6} alkylsulfonyl group, (p-21) a C_{6-10} aryl group, (p-22) a C_{6-10} aryloxy group or (p-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (q) a di-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (q-1) a halogen atom, (q-2) a C_{1-3} alkylenedioxy group, (q-3) a nitro group, (q-4) a cyano group, (q-5) a C_{3-6} cycloalkyl group, (q-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (q-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (q-8) a hydroxyl group, (q-9) an amino group, (q-10) a mono-C_{1-6} alkylamino group, (q-11) a di-C_{1-6} alkylamino group, (q-12) a C_{1-6} alkyl-carbonyl group, (q-13) a carboxyl group, (q-14) a C_{1-6} alkoxy-carbonyl group, (q-15) a carbamoyl group, (q-16) a mono-C_{1-6} alkyl-carbamoyl group, (q-17) a di-C_{1-6} alkyl-carbamoyl group, (q-18) a C_{6-10} aryl-carbamoyl group, (q-19) a sulfo group, (q-20) a C_{1-6} alkylsulfonyl group, (q-21) a C_{6-10} aryl group, (q-22) a C_{6-10} aryloxy group or (q-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (r) an optionally halogenated C_{6-10} aryl-carbamoyl group, (s) an optionally halogenated C_{6-10} aryl-carbonyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group, (x) a C_{2-6} alkenylamino group or (y) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said h terocyclic group being optionally fused

with a benz ne ring,

(31) A c mpound as described in the above item (27) wherein Q^1 and Q^2 are independently a C_{1-6} alkylene group which may have an oxo group,

(32) A compound as described in the above item (27) wherein Q^1 is a C_{1-4} alkylene group and Q^2 is a methylene group,

(33) A compound as described in the above item (27) wherein Ar^3 is a phenyl group optionally substituted with a halogen atom,

(34) A compound as described in the above item (27) wherein Ar^1 and Ar^2 independently represent a C_{6-14} aryl group or a 5- to 7-membered heterocyclic groups having 1 to 3 hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, each of which may have 1 to 3 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl group, and an optionally halogenated C_{1-6} alkoxy group,

(35) A compound as described in the above item (27) wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl,

(36) A compound as described in the above item (27), wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

Q^1 is a C_{1-4} alkylene group; Q^2 is a methylene group;

R^2 is (I) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group or a formyl group or (II) an acyl group represented by the formula:

$$-(C=O)-R^4,\ -SO_2-R^4,\ -(C=O)NR^3R^4 \text{ or } -(C=O)O-R^4$$

wherein R^4 is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group which may have 1 to 5 substituents sel ct d form (a) a hydroxyl group, (b) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (c) a mono-C_{1-6} alkylamino group, (d) a di-C_{1-6} alkylamino group, (e) a carboxyl group, (f) a C_{1-6} alkoxy-carbonyl group, (g) a mono-C_{1-6} alkyl-carbamoyl group, (h) a sulfo group which may be substituted with amino group (i) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (j) a C_{1-6} alkoxy-carbamoyl group, and (k) a carbamoyloxy group.

(iii) a C_{2-6} alkenyl group,

(iv) a C_{6-10} aryl group,

(v) a 5- to 11-membered heterocyclic group having at least one hetero atom selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,

(vi) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkyl-carbonyl group,

(vii) a carboxyl group which may be substituted with a C_{1-6} alkyl group,

(viii) a 5- to 7-membered cyclic amino group which may be substituted with

(a) a C_{1-6} alkyl group optionally substituted with (a-1) a hydroxyl group, (a-2) a di-C_{1-6} alkylamino group, (a-3) a C_{1-6} alkoxy-carbonyl group or (a-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(b) a C_{7-16} aralkyl group, (c) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (c-1) a halogen atom, (c-2) a mono-C_{1-6} alkylamino group, (c-3) a C_{1-6} alkoxy-carbonyl group or (c-4) a 5- to 7-

membered het rocyclic group having 1 to 3 hetero atoms sel cted from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(d) a C_{1-6} alkoxy-carbonyl group, (e) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

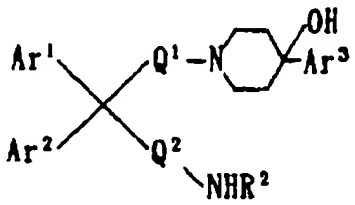
(f) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with a halogen atom or a C_{1-6} alkyl-carbonyl group, (g) an optionally halogenated C_{6-10} aryl-carbamoyl group, (h) an optionally halogenated C_{6-10} aryl carbonyl group or (i) a C_{1-6} alkoxy-carbamoyl group, or

(ix) a C_{6-10} aryloxy group;

R^5 is a hydrogen atom or a C_{1-6} alkyl group; and

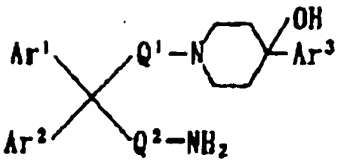
Ar^3 is a phenyl group optionally substituted with a halogen atom,

(37) A process for producing a compound of the formula:



[II]

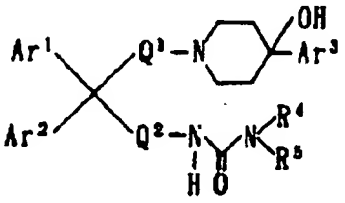
wherein R^2 is an acyl group, and the other symbols have the same meanings as described in the above item (27) or a salt thereof, which comprises subjecting a compound of the formula:



(IX')

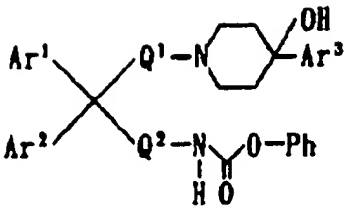
wherein the all symbols have the same meanings as described in the above item (27) or a salt thereof to the acylation reaction,

(38) A process for producing a compound of the formula:



(II')

wherein R^4 represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxy-carbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group or an optionally substituted 5- or 6-membered cyclic amino group; and R^5 is a hydrogen atom or a lower alkyl group, and the other symbols have the same meanings as defined in Claim 27 or a salt thereof, which comprises reacting a compound of the formula:



(X')

wherein Ph is a phenyl group, and the other symbols have the same meanings as defined above or a salt thereof with a compound of the formula:

[XI]

wherein R^4 and R^5 have the same meanings as defined above or a salt thereof,

(39) A composition as described in the above item (1) which is a prophylactic or therapeutic agent for inflammatory diseases,

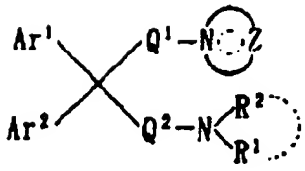
(40) A composition as described in the above item (1) which is a prophylatic or therapeutic agent for allergic diseases,

(41) A composition as described in the above item (1) which is a prophylactic or therapeutic agent for arteriosclerosis, bronchial asthma, atopy, multiple sclerosis or rheumatoid arthritis,

(42) A pharmaceutical composition comprising the compound as described in the above item (27),

(43) A MIP-1α/RANTES receptor antagonist comprising the compound as described in the above item (27),

(44) A method of treating or preventing inflammatory diseases or allergic diseases which comprises administering to a mammal in need an effective amount of a compound of the formula:



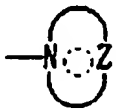
[I]

wherein Ar^1 and Ar^2 independently represent an optionally substituted aromatic group;

Q^1 and Q^2 independently represent an optionally substituted divalent C_{1-6} aliphatic hydrocarbon group which may have oxygen or sulfur within the carbon chain;

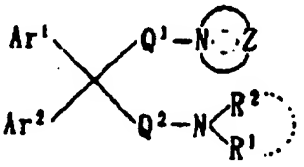
R^1 is a hydrogen atom, an optionally substituted lower alkyl group or an optionally substituted lower alkyl-carbonyl group;

R^2 is an optionally substituted hydrocarbon group or an acyl group, or R^1 and R^2, taken together with the adjacent nitrogen atom, may form an optionally substituted nitrogen-containing heterocyclic ring; and a group of the formula:



is an optionally substituted monocyclic or fused nitrogen-containing heterocyclic ring, or a salt thereof,

(45) Use of a compound of the formula:



[I]

wherein Ar^1 and Ar^2 independently represent an optionally substituted aromatic group;

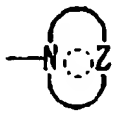
Q^1 and Q^2 independently represent an optionally substituted dival nt C_{1-6} aliphatic hydrocarbon group

which may have oxygen or sulfur within th carbon chain;

R^1 is a hydrogen atom, an optionally substituted lower alkyl group or an optionally substituted lower alkyl-carbonyl group;

R^2 is an optionally substituted hydrocarbon group or an acyl group, or R^1 and R^2, taken together with the adjacent nitrogen atom, form an optionally substituted nitrogen-containing heterocyclic ring; and

a group of the formula:



is an optionally substituted monocyclic or fused nitrogen-containing heterocyclic ring or a salt thereof, for the manufacture of a medicament for treating or preventing inflammatory diseases or allergic diseases, and

(46) A compound as described in the above item (27) which is Examples

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(piperidin-4-yl)urea,

Ethyl 4-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino] piperidino-4-oxobutyrate,

N-Ethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino-1-piperidinecarboxamide,

N-Ethoxycarbonylmethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]aminocarbonyl-amino-1-piperidinecarboxamide,

Ethyl 3-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino] piperidino-3-oxopropionate,

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(1-ethylpip ridin-4-yl)urea,

1-[(Piperidin-4-yl)carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diph nylpentane,
1-[[(N-Ethylcarbamoyl)piperidin-4-yl]carboamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[N-(Ethoxycarbonylacetyl)piperidin-4-yl]carboamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[N-(3-Methoxycarbonylpropionyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane or a salt thereof.

Detailed description

The aromatic group of the "optionally substituted aromatic group" for Ar^1, Ar^2 and Ar^3 includes, for example, "aromatic hydrocarbon groups" and "heteroaromatic groups" and these groups may have any number (preferably 1 to 5, more preferably 1 to 3, further more preferably 1 or 2) of substituents in any substitutable position.

The "aromatic hydrocarbon group" mentioned above includes, for example, monocyclic or fused polycyclic aromatic hydrocarbon groups having 6 to 14 carbon atoms. Specific examples thereof include C_{6-14} aryl groups such as phenyl, 1-naphthyl, 2-naphthyl, indenyl, anthryl, etc. Among them, phenyl, 1-naphthyl and 2-naphthyl are preferred, and phenyl is particularly preferred.

The "heteroaromatic group" mentioned above includes, for example, 5- to 11-membered monocyclic or fused heteroaromatic groups having at least one (e.g. 1 to 4, preferably 1 to 3, more preferably 1 or 2) of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to a carbon atom. Specific examples thereof include aromatic heterocyclic group such as thiophene, benzo[b]thiophene, benzo[b]furan, b nzimidazole,

benzoxaz le, benz thiazole, b nzisothiazole, naphtho[2,3-b]thiophene, thianthrene, furan, isoindolizine, xanthrene, phenoxathiin, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indol, isoindol, 1H-indazole, purine, 4H-quinolizine, isoquinoline, quinoline, phtharazine, naphthyridine, quinoxaline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, isothiazole, phenothiazine, isoxazole, furazane, phenoxazine, isochroman, etc., or a monovalent group obtained by eliminating any hydrogen from a ring formed by condensing these rings (preferably monocyclic heterocycle mentioned above) with one or a plurality (preferably 1 or 2, more preferably 1) of aromatic rings (e.g. aromatic hydrocarbon group, preferably benzene ring, etc.). The preferred "aromatic heterocyclic group" include, for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, 2-thienyl, 3-thienyl, etc. The more preferred one include, for example, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl, 2-benzothiazolyl, etc. Among them, 2-pyridyl is commonly used.

The substituent that may be present on the "optionally substituted aromatic ring in any position" for Ar^1, Ar^2 and Ar^3 includes, for example, a halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), a nitro group, a cyano group, an optionally halogenated lower alkyl group, an optionally halogenated lower alkenyl group, an optionally halogenated lower alkynyl group, a

lower cycloalkyl group (.g. C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclop ntyl, cyclohexyl, etc.), an optionally halogenated lower alkoxy group, an optionally halogenated lower alkylthio group, a hydroxyl group, an amino group, a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), a 5- to 7-membered cyclic amino group (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, etc.), an acylamino group, a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a carbamoyl group, a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.), a di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.), an aryl-carbamoyl group (e.g. C_{6-10} aryl-carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, etc.), a sulfo group, a lower alkylsulfonyl group (e.g. C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), an aryl group (e.g. C_{6-10} aryl such as phenyl, naphthyl, etc.) or an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.).

The "optionally halogenated lower alkyl group" mentioned above includes, for example, a lower alkyl group optionally having 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.) (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, p ntyl, hexyl, etc.).

Specific examples th r of include methyl, chloromethyl, difluorom thyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

The "optionally halogenated lower alkenyl group" and "optionally halogenated lower alkynyl group" include, for example, a lower alkenyl group optionally having 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.) (e.g. C_{2-6} alkenyl such as vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl, 5-hexen-1-yl, etc.) or a lower alkynyl group optionally having 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.) (e.g. C_{2-6} alkynyl such as 2-butyn-1-yl, 4-pentyn-1-yl, 5-hexyn-1-yl, etc.).

The "optionally halogenated lower alkoxy group" include, for example, a lower alkoxy group optionally having 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.) (e.g. C_{1-6} alkoxy such as methoxy, ethoxy, butoxy, propoxy, isoprpoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.). Specific examples thereof include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, n-propoxy, isopropoxy, n-butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

The "optionally halogenated lower alkylthio group" include, for example, a lower alkylthio group optionally having 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.) (e.g. C_{1-6} alkylthio such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, s c-butylthio, tert-butylthi , etc.). Specific examples thereof include methylthio,

difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc.

The "acylamino group" include, for example, $-NHCOOR^3$, $-NHCONHR^3$, $-NHCOR^3$ or $-NHSO_2R^3$ (R^3 is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, preferably optionally substituted hydrocarbon group).

The substituent that may be present on the "optionally substituted aromatic ring in any position" for Ar^1, Ar^2 and Ar^3 includes, for preferred example, a halogen atom, an optionally halogenated C_{1-6} alkyl group, optionally halogenated C_{1-6} alkoxy group, a C_{1-3} alkylenedioxy group (particularly methylenedioxy), a cyano group, a hydroxyl group, etc. Among them, a halogen atom, an optionally halogenated C_{1-6} alkyl group and an optionally halogenated C_{1-6} alkoxy group are particularly preferred, and an halogen atom is commonly used.

The preferred one for Ar^1 and Ar^2 include independently, for example, optionally halogenated phenyl (e.g. phenyl, 4-chlorophenyl, 4-fluorophenyl, etc.) 2-pyridyl, 3-pyridyl and 4-pyridyl. Among them, phenyl and 2-pyridyl are more preferred. As Ar^1 and Ar^2, phenyl is commonly used independently.

As Ar^3, a C_{1-3} alkyl group optionally substituted with 1 to 3 halogen atoms, a C_{1-3} alkoxy group optionally substituted with 1 to 3 halogen atoms or a phenyl group optionally substituted with halogen (preferably, chlorine, fluorine, etc.) (e.g. 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-dichlorophenyl, 3,5-difluorophenyl, 4-trifluoromethylphenyl, etc.) or 2-pyridyl, 3-pyridyl, 4-pydridyl are preferred. Among them, optionally halogenated phenyl is preferred and 4-chloroph nyl is

particularly pref rr d.

The "optionally substituted hydrocarbon group" for R^2 and R^3 represents a group obtained by eliminating one hydrogen from a hydrocarbon compound and examples thereof include acyclic or cyclic hydrocarbon groups such as alkyl, alkenyl, cycloalkyl, aryl, aralkyl, etc. Preferred are acyclic or cyclic hydrocarbon groups having 1 to 16 carbon atoms as described below.

(a) a lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.)

(b) a lower alkenyl group (C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.)

(c) a lower alkynyl group (C_{2-6} alkynyl such as propargyl, ethynyl, butynyl, 1-hexynyl, etc.)

(d) a lower cycloalkyl group (e.g. C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl optionally fused with a benzene ring optionally having 1 to 3 lower alkoxy groups (e.g. C_{1-6} alkoxy such as methoxy, etc.))

(e) an aryl group (e.g. C_{6-17} aryl group such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-indenyl, 2-anthryl, etc., preferably phenyl)

(f) an aralkyl group (e.g. C_{7-16} aralkyl group such as benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc., preferably benzyl). Among them, a lower alkyl group, an aryl group and an aralkyl group are preferred.

Especially, a lower alkyl group is preferred.

The substituent which may be present on the "optionally substituted hydrocarbon group" for R^2 and R^3 may have 1 to 5, preferably 1 to 3 substituents in

substitutable positions, and wh r the number of substitu nts is 2 or more, the substituent groups may be the same or different.

The substituent that may be present on the "optionally substituted hydrocarbon group" includes, for example, a halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), a nitro group, a cyano group, an optionally halogenated lower alkyl group, a lower cycloalkyl group (e.g. C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), an optionally halogenated lower alkoxy group, an optionally halogenated lower alkylthio group, a hydroxyl group, an amino group, a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, etc.), a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, ethylcarbonyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a carbamoyl group, a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.), a di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.), a sulfo group, a lower alkylsulfonyl group (e.g. C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), an aryl group (e.g. C_{6-10} aryl such as phenyl, naphthyl, etc.), an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.) or a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxyg n atom and a sulfur atom in

addition to a carbon atom or a group fused with a benzene ring.

The "optionally halogenated lower alkyl group," "optionally halogenated lower alkoxy group" and "optionally halogenated lower alkylthio group" include the same substituents as mentioned for the aromatic group.

The "aryl group (preferably phenyl) and aryloxy group (preferably phenyloxy)" may have the same substituents mentioned for the "optionally substituted aromatic group in any position."

The "5- to 7-membered heterocyclic group or a group fused with a benzene ring" include, for example, 5- to 7-membered (preferably 5- or 6-membered) heterocyclic group having 1 to 3, preferably 1 or 2 hetero atoms of 1 or 2 kinds selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to a carbon atom. Specific examples thereof include 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholino, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, etc. These groups may be fused with a benzene ring in any position. Furthermore, the "5- to 7-membered heterocyclic group or a group fused with a benzene ring" may have 1 to 3 substituents in substitutable positions.

The substituent include substituents that may be present on the "optionally substituted hydrocarbon group" for Ar^1, Ar^2 and Ar^3. The preferred one include, for example, a halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), a nitro group, a cyano group, an optionally hal genated lower alkyl group, a lower

cycloalkyl group (.g. C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), an optionally halogenated lower alkoxy group, an optionally halogenated lower alkylthio group, a hydroxyl group, an amino group, a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), a 5- to 7-membered cyclic amino group (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, etc.), a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a carbamoyl group, a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.), a di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.), an aryl-carbamoyl group (e.g. C_{6-10} aryl-carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, etc.), a sulfo group, a lower alkylsulfonyl group (e.g. C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), an aryl group (e.g. C_{6-10} aryl such as phenyl, naphthyl, etc.) or an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.).

The "optionally halogenated lower alkyl group," "optionally halogenated lower alkoxy group" and "optionally halogenated lower alkylthio group" include the same substituents mentioned for the "optionally substituted aromatic group" for Ar^1, Ar^2 and Ar^3.

The preferred "optionally substituted hydrocarbon"

for R^2 is a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group, or a formyl group.

The "acyl group" for R^2 includes, for example, $-(C=O)-R^4$, $-SO_2-R^4$, $-SO-R^4$, $-(C=O)NR^5-R^4$, $-(C=O)O-R^4$, $-(C=S)O-R^4$, $-(C=S)NR^5-R^4$ (R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, butyryl, etc.), a carboxyl group, an optionally substituted lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), an optionally substituted mono-lower alkylaminocarbonyl group (e.g. C_{1-6} alkyl-carbamoyl such as methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, butylaminocarbonyl, etc.), an optionally substituted di-lower alkylaminocarbonyl group (e.g. C_{1-6} alkyl-carbamoyl such as dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, dibutylaminocarbonyl, etc.), an optionally substituted 5- or 7-membered cyclic amino group (e.g. 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-pyrrolidinyl, 3-pyrrolidinyl, 2-piperazyl, etc.) or an optionally substituted aryloxy group (e.g. C_{6-10} aryloxy group such as phenyloxy etc.); and R^5 is a hydrogen atom or a lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc., where C_{1-3} alkyl such as methyl, ethyl, propyl, isopropyl, etc. are particularly preferred)).

Among them, $-(C=O)-R^4$, $-SO_2-R^4$, $-SO-R^4$, $-(C=O)NR^5-R^4$ and $-(C=O)O-R^4$ (R^4 and R^5 have the same meanings as defined above) are preferred, and $-(C=O)-R^4$, $-SO_2-R^4$,

$-(C=O)NR^5-R^4$ and $-(C=O)O-R^4$ (R^4 and R^5 have the same meanings as defined above) are more pr ferr d. Especially preferred is $-(C=O)-R^4$ or $-(C=O)NH-R^4$ (R^4 is the same meanings as defined above).

The preferred example of R^2 is (1) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group or a carboxyl group, a C_{1-6} alkyl-carbonyl group or a formyl group, or (2) acyl group.

Especially, acyl group is commonly used.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^4 represents a group obtained by eliminating one hydrogen from a hydrocarbon compound, and examples thereof include acyclic or cyclic hydrocarbon groups such as alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, etc. Specific examples thereof include the same substituents mentioned for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2 and R^3. Among them, acyclic or cyclic hydrocarbon groups having 1 to 16 carbon atoms are preferred, particularly lower (C_{1-6}) alkyl group, lower (C_{2-6}) alkenyl group or lower (C_{6-10}) aryl group is preffered. A lower (C_{1-6}) alkyl group is commonly used.

The preferred substituent which may be present on the "hydrocarbon group", "heterocyclic group", "lower alkyl-carbonyl group", "a carboxyl group", "lower alkoxy-carbonyl group", "mono-lower alkylaminocarbonyl group", "di-lower alkylaminocarbonyl group", "5- or 7-membered cyclic amino group" and "aryloxy group" for R^4 includes, for example, (i) a halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), (ii) a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), (iii) a nitro group, (iv) a cyano group, (v) a C_{1-6} alkyl group optionally substituted with (1) a halogen atom, (2) a

C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (vi) a C_{3-6} cycloalkyl group, (vii) an optionally halogenated lower alkoxy group, (viii) an optionally halogenated lower alkylthio group, (ix) a C_{7-16} aralkyl group, (x) a hydroxyl group, (xi) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (xii) a mono-lower alkylamino group (e.g. C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), (xiii) a di-lower alkylamino group (e.g. di-lower alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), (xiv) a 5- or 7-membered cyclic amino group optionally having hydroxy or oxo (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridon-1-yl, etc.), (xv) a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-}

$_6$ alkoxy gr up optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xvi) a carboxyl group, (xvii) a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), (xviii) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xix) a carbamoyl group, (xx) a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.) whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl

group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xxi) a di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.) whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xxii) an optionally halogenated aryl-carbamoyl group (e.g. C_{6-10} aryl-carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, etc.), (xxiii) an optionally halogenated aryl-carbonyl group (e.g. C_{6-10} aryl-carbonyl such as phenylcarbonyl, haphthylcarbonyl, etc.), (xxiv) a sulfo group optionally substituted with amin group, (xxv) a lower alkylsulfonyl group (e.g.

C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), (xxvi) an aryl group (e.g. C_{6-10} aryl such as phenyl, naphthyl, etc.), (xxvii) an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.), (xxviii) a C_{2-6} alkenylamino, (xxix) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xxx) a sulfamoyl group, (xxxi) a mono-lower alkyl-sulfamoyl group(e.g. mono-C_{1-6} alkyl-sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, etc.), (xxxii) a di-lower alkyl-sulfamoyl group (e.g. di-C_{1-6} alkyl-sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl, etc.), (xxxiii) a lower alkoxy-carbamoyl group (e.g. C_{1-6} alkoxy-carbamoyl such as methoxycarbamoyl, ethoxycarbamoyl, etc.), and (xxxiv) a carbamoyloxy group.

The preferred one includes, for example, a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.); a nitro group; a cyano group; a C_{1-6} alkyl group optionally substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5-

to 7-memb red heterocyclic group having 1 to 3 hetero atoms sel cted from nitr gen, oxyg n and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring; a C_{3-6} cycloalkyl group; an optionally halogenated lower alkoxy group; an optionally halogenated lower alkylthio group; a hydroxyl group; a C_{7-16} aralkyl group; an amino group optionally substituted with a C_{1-6} alkyl-carbonyl group; a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.); a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.); a 5- or 7-membered cyclic amino group optionally having hydroxy or oxo (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridon-1-ly, etc.); a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.) whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon

atoms, said heterocyclic group being optionally fused with a benzene ring; a carboxyl group; a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc,); a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring; a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring; an optionally halogenated C_{6-10} aryl-carbamoyl group; an optionally halogenated C_{6-10} aryl-carbonyl group; a sulfo group which may substituted with amino group; an aryl group (e.g. C_{6-10} aryl such as phenyl, naphthyl, etc.); an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.); a C_{2-6} alkenylamino; a 5- to 7-membered h terocyclic group having 1 to 3 hetero atoms selected

from nitrog n, oxygen and sulfur in addition to carbon atoms, said h terocyclic group being optionally fused with a benzene ring; a sulfamoyl group; a mono-lower alkyl-sulfamoyl group (e.g. C_{1-6} alkyl-sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, etc.); a di-lower alkyl-sulfamoyl group (e.g. di-C_{1-6} alkyl-sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl, etc.); a lower alkoxy-carbamoyl group (e.g. C_{1-6} alkoxy-carbamoyl such as methoxycarbamoyl, ethoxycarbamoyl, etc.); and a carbamoyloxy group.

The more preferred one includes, for example, (i) a C_{1-6} alkyl group optionally substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (ii) a C_{3-6} cycloalkyl group, (iii) an C_{7-16} aralkyl group, (iv) a hydroxyl group, (v) an amino group optionally having a C_{1-6} alkoxy, (vi) a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc), (vii) a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such

as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), (viii) a 5- or 7-membered cyclic amino group optionally having hydroxyl or oxo (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridon-1-yl, etc.), (ix) a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.) whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (x) a carboxyl group, (xi) a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), (xii) formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xiii) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkyl nedioxy group, (3) a

nitro gr up, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xiv) an optionally halogenated C_{6-10} aryl-carbamoyl group, (xv) an optionally halogenated C_{6-10} aryl-carbonyl group, (xvi) a sulfo group which may substituted with amino group, (xvii) an aryl group (e.g. C_{6-10} aryl such as phenyl, naphthyl, etc.), (xviii) an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.), (xix) a C_{2-6} alkenylamino, (xx) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring; (xxi) a lower alkoxy-carbamoyl group (e.g. C_{1-6} alkoxy-carbamoyl such as methoxycarbamoyl, ethoxycarbamoyl, etc.), and (xxii) a carbamoyloxy group.

The "optionally halogenated lower alkoxy group" and "optionally halogenated lower alkylthio group" includes, for example, the same groups as those mentioned for the substituents of the "optionally substituted aromatic group" for Ar^1, Ar^2 and Ar^3.

The "heterocyclic group" of the "optionally substituted h terocyclic group" for R^3 and R^4 include, for example, a 5- to 11-membered (cyclic or bicyclic) heterocyclic group having at least one (e.g. 1 to 4, preferably 1 to 3, more preferably 1 or 2) hetero atoms of 1 or 2 kinds selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to a carbon atom. Examples thereof include 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholinyl, non-aromatic heterocyclic group such as 3- or 4-azepinyl (preferably 5- to 7-membered saturated cyclic amino group such as 1- or 2-piperazinyl) and heteroaromatic groups (e.g. 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 4-quinolyl, 8-quinolyl, 4-isoquinolyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 2-imidazolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, i-indolyl, 2-isoindolyl, etc. Among them, a heteroaromatic group or a 5- to 7-membered saturated cyclic amino group is preferred. The more preferred one includes, for example, a 5- or 7-membered heteroaromatic group having 1 to 3 hetero atoms of 1 or 2 kinds selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to a carbon atom (e.g. 2-thienyl, 3-thienyl, 2-pyridyl, 4-pyridyl, etc.) and a 5- to 7-membered saturated cyclic amino group.

Especially, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl or morpholinyl is preferred.

The substituent which may substituted on the "optionally substituted heterocyclic group" includes, for example, the same number of the same substituents as mentioned for the "optionally substituted hydrocarbon group" for R^4.

Preferred examples of R^4 is (i) a hydrogen atom, (ii) a C_{1-6} alkyl group which may have 1 to 5

substituents selected from (a) a hydroxyl group, (b) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (c) a mono-C_{1-6} alkylamino group, (d) a di-C_{1-6} alkylamino group, (e) a carboxyl group, (f) a C_{1-6} alkoxy-carbonyl group, (g) a mono-C_{1-6} alkyl-carbamoyl group, (h) a sulfo group which may be substituted with amino group (i) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (j) a C_{1-6} alkoxy-carbamoyl group, and (k) a carbamoyloxy group.

(iii) a C_{2-6} alkenyl group,

(iv) a C_{6-10} aryl group,

(v) a 5- to 11-membered heterocyclic groups having at least one hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,

(vi) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkyl-carbonyl group,

(vii) a carboxyl group which may be substituted with a C_{1-6} alkyl group,

(viii) a 5- to 7-membered cyclic amino group which may be substituted with

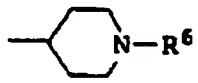
(a) a C_{1-6} alkyl group optionally substituted with (a-1) a hydroxyl group, (a-2) a di-C_{1-6} alkylamino group, (a-3) a C_{1-6} alkoxy-carbonyl group or (a-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(b) a C_{7-16} aralkyl group, (c) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (c-1) a halogen atom, (c-2) a mono-C_{1-6} alkylamino group, (c-3) a C_{1-6} alkoxy-carbonyl group or (c-4) a 5- to 7-membered h t rocyclic group having 1 to 3 hetero atoms

selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(d) a C_{1-6} alkoxy-carbonyl group, (e) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(f) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with a halogen atom or a C_{1-6} alkyl-carbonyl group, (g) an optionally halogenated C_{6-10} aryl-carbamoyl group, (h) an optionally halogenated C_{6-10} aryl-carbonyl group or (i) a C_{1-6} alkoxy-carbamoyl group, or
(ix) a C_{6-10} aryloxy group.

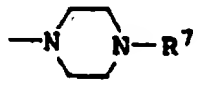
More preferred example of R^4 is a group represented by the formula:

(1)



or

(2)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with
(b-1) a halogen atom, (b-2) a C_{1-3} alkylenedioxy group, (b-3) a nitro group, (b-4) a cyano group, (b-5) a C_{3-6} cycloalkyl group, (b-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (b-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (b-8) a hydroxyl group, (b-9) an amino group, (b-10) a mono-C_{1-4}

alkylamino group, (b-11) a di-C_{1-6} alkylamino group, (b-12) a C_{1-6} alkyl-carbonyl group, (b-13) a carboxyl group, (b-14) a C_{1-6} alkoxy-carbonyl group, (b-15) a carbamoyl group, (b-16) a mono-C_{1-6} alkyl-carbamoyl group, (b-17) a di-C_{1-6} alkyl-carbamoyl group, (b-18) a C_{6-10} aryl-carbamoyl group, (b-19) a sulfo group, (b-20) a C_{1-6} alkylsulfonyl group, (b-21) a C_{6-10} aryl group, (b-22) a C_{6-10} aryloxy group or (b-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{3-6} cycloalkyl group, (d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (e) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (f) a C_{7-16} aralkyl group, (g) a hydroxyl group, (h) an amino group, (i) a mono-C_{1-6} alkylamino group, (j) a di-C_{1-6} alkylamino group, (k) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (k-1) a halogen atom, (k-2) a C_{1-3} alkylenedioxy group, (k-3) a nitro group, (k-4) a cyano group, (k-5) a C_{3-6} cycloalkyl group, (k-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (k-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (k-8) a hydroxyl group, (k-9) an amino group, (k-10) a mono-C_{1-6} alkylamino group, (k-11) a di-C_{1-6} alkylamino group, (k-12) a C_{1-6} alkyl-carbonyl group, (k-13) a carboxyl group, (k-14) a C_{1-6} alkoxy-carbonyl group, (k-15) a carbamoyl group, (k-16) a mono-C_{1-6} alkyl-carbamoyl group, (k-17) a di-C_{1-6} alkyl-carbamoyl group, (k-18) a C_{6-10} aryl-carbamoyl group, (k-19) a sulfo group, (k-20) a C_{1-6} alkylsulfonyl group, or (k-21) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said

heterocyclic group being optionally fused with a benzene ring, (l) a carboxyl group, (m) a C_{1-6} alkoxy-carbonyl group, (n) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms seleced from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (o) a carbamoyl group, (p) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (p-1) a halogen atom, (p-2) a C_{1-3} alkylenedioxy group, (p-3) a nitro group, (t-4) a cyano group, (p-5) a C_{3-6} cycloalkyl group, (p-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (p-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (p-8) a hydroxyl group, (p-9) an amino group, (p-10) a mono-C_{1-6} alkylamino group, (p-11) a di-C_{1-6} alkylamino group, (p-12) a C_{1-6} alkyl-carbonyl group, (p-13) a carboxyl group, (p-14) a C_{1-6} alkoxy-carbonyl group, (p-15) a carbamoyl group, (p-16) a mono-C_{1-6} alkyl-carbamoyl group, (p-17) a di-C_{1-6} alkyl-carbamoyl group, (p-18) a C_{6-10} aryl-carbamoyl group, (p-19) a sulfo group, (p-20) a C_{1-6} alkylsulfonyl group, (p-21) a C_{6-10} aryl group, (p-22) a C_{6-10} aryloxy group or (p-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (q) a di-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (q-1) a halogen atom, (q-2) a C_{1-3} alkylenedioxy group, (q-3) a nitro group, (q-4) a cyano group, (q-5) a C_{3-6} cycloalkyl group, (q-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (q-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (q-8) a hydroxyl group, (q-9) an amino group, (q-10) a mono-C_{1-6} alkylamino group, (q-11) a di-C_{1-6}

alkylamino group, (q-12) a C_{1-6} alkyl-carbonyl group, (q-13) a carboxyl group, (q-14) a C_{1-6} alkoxy-carbonyl group, (q-15) a carbamoyl group, (q-16) a mono-C_{1-6} alkyl-carbamoyl group, (q-17) a di-C_{1-6} alkyl-carbamoyl group, (q-18) a C_{6-10} aryl-carbamoyl group, (q-19) a sulfo group, (q-20) a C_{1-6} alkylsulfonyl group, (q-21) a C_{6-10} aryl group, (q-22) a C_{6-10} aryloxy group or (q-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (r) an optionally halogenated C_{6-10} aryl-carbamoyl group, (s) an optionally halogenated C_{6-10} aryl-carbonyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group, (x) a C_{2-6} alkenylamino group or (y) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring.

Preferred example of R^6 and R^7 is, independently, (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with

(b-1) a hydroxyl group, (b-2) a di-C_{1-6} alkylamino group, (b-3) a C_{1-6} alkoxy-carbonyl group, or (b-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{7-16} aralkyl group, (d) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (d-1) a halogen atom, (d-2) a mono-C_{1-6} alkylamino group, (d-3) a C_{1-6} alkoxy-carbonyl group, or (d-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon

atoms, said heterocyclic group being optionally fused with a benzen ring, (e) a C_{1-6} alkoxy-carbonyl group, (f) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (g) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (g-1) a halogen atom, or (g-2) a C_{1-6} alkyl-carbonyl group, (h) an optionally halogenated C_{6-10} aryl-carbamoyl group, (i) an optionally halogenated C_{6-10} aryl-carbonyl group, or (j) a C_{6-10} aryloxy group.

The "lower alkyl group" of the "optionally substituted lower alkyl group" for R^1 is, for example, a straight-chain or branched lower alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "lower alkyl-carbonyl group" of the "optionally substituted lower alkyl-carbonyl group" for R^1 is, for example, an C_{1-6} alkyl-carbonyl group such as methylcarbonyl, ethylcarbonyl, butylcarbonyl, etc.

The substituent which may be present on the "lower alkyl group" and "lower alkyl-carbonyl group" includes, for example, the same substituents as mentioned for the "optionally substituted hydrocarbon group" for R^2.

Preferred examples of R^1 include a hydrogen atom or a lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.). Among them, a hydrogen atom and methyl are particularly preferred.

Especially preferred for R^1 is a hydrogen atom.

The "nitrogen-containing heterocyclic group formed by bonding R^1 and R^2 together with adjacent nitrogen" is, for example, a 4- to 8-memb red ring optionally

having at least one nitrogen atom and 1 to 3 (preferably 1 to 2) ring-constituting atoms such as an oxygen atom, a sulfur atom, etc. in addition to a carbon atom, or the 4- to 8-membered ring fused with a benzene ring.

Examples thereof include an aromatic heterocyclic group (e.g. 1-pyrrolyl, 1-imidazolyl, 1-indolyl, 1-pyrazolyl, 2-isoindolyl, 1-indazolyl, etc.), a cyclic amino group (e.g. morpholino, piperidino, 1-piperazinyl, 1-pyrrolidinyl, 1-pirazolidinyl, 1-azepinyl, etc.) or the cyclic amino group fused with a benzene ring (e.g. 1-indolinyl, 2-isoindolinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydro-isoquinolin-2-yl, 3-benzazepin-3-yl, etc.) or a lactam or an imide group (e.g. phthalimide, succinimide, 2-pyrrolidon-1-yl, 2-pyridon-1-yl, 2-quinolon-1-yl, etc.).

The "nitrogen-containing heterocyclic group formed by bonding R^1 and R^2 together with adjacent nitrogen" may have the same substituent as that may be present on the "optionally substituted hydrocarbon group" for R^2. The group fused with a benzene ring may have one or plurality (preferably 1 to 5, more preferably 1 to 3, further more preferably 1 or 2) of substituents selected from a halogen group (e.g. fluorine, chlorine, bromine, iodine, etc.), a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), a nitro group, a cyano group, an optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, an optionally halogenated lower alkylthio group, a hydroxyl group, an amino group, a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dim thylamino, di thylamino, dipropylamino,

dibutylamino, etc.), a carboxyl group, a lower alkocycarbonyl group (.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.) or a carbamoyl group in any position on the benzene ring.

The "optionally halogenated lower alkyl group," "optionally halogenated lower alkoxy group" and "optionally halogenated lower alkylthio group" include the same groups as mentioned for the substituents of the "optionally substituted aromatic group" for Ar^1, Ar^2 and Ar^3.

As the "nitrogen-containing heterocyclic group" of the "nitrogen-containing heterocyclic group formed by bonding R^1 and R^2 together with adjacent nitrogen," "1-piperazinyl" is preferred. The "1-piperazinyl" having a substituent on a nitrogen atom at the 4-position is preferred.

The preferred substituent on the nitrogen atom at the 4-position of the "1-piperazinyl" includes, for example, a lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), aryl (e.g. C_{6-14} aryl such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-indenyl, 2-anthryl, etc., preferably phenyl), 2-pyridyl, 3-pyridyl, 4-pyridyl, an aralkyl group (e.g. C_{7-16} aralkyl such as benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc., preferably benzyl), a phenacyl group or a nicotinoyl group.

Furthermore, an aryl group, an aralkyl group, a phenacyl group and a nicotinoyl group may have one or plurality (preferably 1 to 5, more preferably 1 to 3, further more preferably 1 or 2) of substituents selected from a halogen atom (e.g. fluorine, chlorine, bromine, iodine, tc.), a low r alkylenedioxy group

(e.g. C_{1-3} alkylenedi xy such as methylen dioxy, ethylenedioxy, etc.), a nitro group, a cyano group, optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, an optionally halogenated lower alkylthio group, a hydroxyl group, an amino group, a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.) or a carbamoyl group in any position on the benzene ring.

The "optionally halogenated lower alkyl group," "optionally halogenated lower alkoxy group" and "optionally halogenated lower alkylthio group" include the same groups mentioned for the substituents of the "optionally substituted aromatic group" for Ar^1, Ar^2 and Ar^3.

The term "divalent aliphatic hydrocarbon group" of the "optionally substituted divalent aliphatic hydrocarbon group optionally having oxygen or sulfur in the carbon chain" for Q^1 and Q^2 means a group obtained by eliminating each one hydrogen (two hydrogens in total) bound to the same or different carbon atoms from the saturated or unsaturated aliphatic hydrocarbon and preferably have not more than 6 carbon atoms. Specific examples thereof include the following:

(i) a C_{1-6} alkylene group (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, etc.)

(ii) a C_{2-6} alkenylene group (e.g. $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-CH_2-$, $-(CH_2)_2-CH=CH-CH_2-$, $-(CH_2)_2-CH=CH-(CH_2)_2-$, $-(CH_2)_3-CH=CH-CH_2-$, tc.)

(iii) a C_{2-6} alkynylene group (.g. $-C\equiv C-$, $-C\equiv C-CH_2-$, $-CH_2-C\equiv C-CH_2-$, $-(CH_2)_2-C\equiv C-CH_2-$, $-(CH_2)_2-C\equiv C-(CH_2)2-$, $-(CH_2)_3-C\equiv C-CH_2-$,etc).

Preferred one is a C_{1-6} alkylene group and particularly preferred one is a C_{1-3} alkylene group.

These groups may have an oxygen atom or an optionally oxidized sulfur atom in the carbon atom, or any carbon atom may be substituted with an oxo group or a thioxo group in the carbon chain.

For example, a group represented by the formula $-(CH_2)a-T-(CH_2)m-$ [wherein T is a bond, an oxygen atom or an optionally oxidized sulfur atom; and a and m independently represent an integer of 0 to 5 and the total of them is 1 to 6].

Preferred examples of Q^1 and Q^2 is a C_{1-6} alkylene group optionally having an oxo group, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2CO-$, $-CH_2CO-$, $-CO-$, etc.

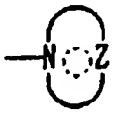
Preferred examples of Q^1 is a C_{1-4} alkylene group optionally having an oxo group, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2CO-$ and-CH_2CO-. Particularly preferred are $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_2CO-$ and $-CH_2CO-$. Among them, $-(CH_2)_3-$ is commonly used.

Preferred examples of Q^2 are $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2CO-$, $-CH_2CO-$ and $-CO-$. Particularly preferred are $-CH_2-$, $-(CH_2)_2-$ and $-(CH_2)_3-$. Among them, $-CH_2-$ is commonly used.

The divalent aliphatic hydrocarbon group may have ether oxygen or sulfur in the carbon chain, and examples thereof include $-CH_2-O-CH_2-$, $-CH_2-O-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-(CH_2)_2-CH_2-O-CH_2-CH_2-$, $(CH_2)_2-CH_2-O-CH_2-(CH_2)_2-$, $(CH_2)_3-CH_2-O-CH_2-CH_2-$,

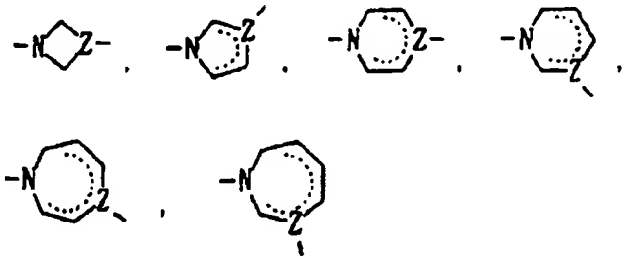
$-CH_2-S-CH_2-$, $-CH_2-S-CH_2-CH_2-$, $-CH_2-CH_2-S-CH_2-CH_2-$, $-(CH_2)_2-CH_2-S-CH_2-CH_2-$, $(CH_2)_2-CH_2-S-CH_2-(CH_2)_2-$, $-(CH_2)_3-CH_2-S-CH_2-CH_2-$, etc. A sulfur atom may be sulfoxide or sulfon.

The "optionally substituted monocyclic or fused nitrogen-containing heterocyclic ring" represented by a group of the formula:

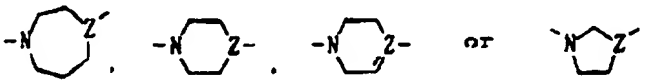


may have 1 or 2 unsaturated bonds and represents a monocyclic 4- to 9-membered ring or bicyclic 6- to 14-membered ring optionally having 1 or 2 substituents in any position other than N and Z.

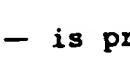
The preferred "monocyclic nitrogen-containing heterocyclic ring" of the "optionally substituted monocyclic nitrogen-containing heterocyclic ring" includes, for example, the following:



(wherein Z has the same meanings as defined above; and ..... represents a single bond or a double bond). Among them,



is preferred.

Especially,  is preferred.

These monocyclic nitrog n-containing heterocyclic

ring may be fused with a 3- to 10-membered cyclic hydrocarbon group, for exampl , a lower cycloalkane group (e.g. C_{3-8} cycloalkane such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, etc.), a lower cycloalkene group (e.g. C_{3-6} cycloalkene such as cyclopropene, cyclopentene, cyclohexene, etc.) or an aryl group (e.g. C_{6-10} aryl such as benzene, etc.) to form a bicyclic 6- to 14-membered nitrogen-containing heterocycle. Among them, pyrrolidine, piperidine, azepine or one of these three groups fused with a benzine ring are preferred. Particularly preferred is piperidine.

Examples of the substituent which may present on the monocyclic or fused nitrogen-containing heterocyclic ring include an optionally substituted lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), an optionally substituted lower alkoxy group (e.g. C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), an optionally substituted lower alkylthio group (e.g. C_{1-6} alkylthio such as methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, etc.), a hydroxyl group, an amino group, a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarb nyl, butoxycarbonyl, etc.),

a carbamoyl group, a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as m thylcarbamoyl, ethylcarbamoyl, etc.), a di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.,), an aryl-carbamoyl group (e.g. C_{6-10} aryl-carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, etc.), a sulfo group, a lower alkylsulfonyl group (e.g. C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), an aryl group (C_{6-10} aryl such as phenyl, naphthyl, etc.) or an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.).

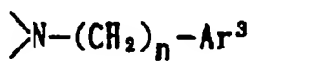
The substituent which may present on the "optionally substituted lower alkyl group," "optionally substituted lower alkoxy group" and "optionally substituted lower alkylthio group" include, for examples, a lower alkoxy group (e.g. C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), a lower alkylthio group (e.g. C_{1-6} alkylthio such as methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, etc.), a hydroxyl group, an amino group, a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a carbamoyl group, a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.), a

di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.,), an aryl-carbamoyl group (e.g. C_{6-10} aryl-carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, etc.), a sulfo group, an alkylsulfonyl group(e.g. C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), an aryl group(C_{6-10} aryl such as phenyl, naphthyl, etc.) or an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.).

Z is, for example, the following:

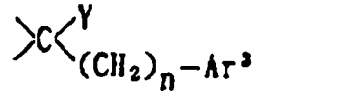
[1] An optionally substituted 1, 2-phenylene,

[2] A group of the formula:



[wherein Ar^3 has the same meanings as defined above; and n is an integer of 0 to 3],

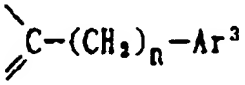
[3] A group of the formula:



[wherein Ar^3 and n have the same meanings as defined above; and Y is an hydrogen atom, an optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, an optionally halogenated lower alkylthio group, a hydroxyl group, a cyano group, an alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), a lower alkyl-carbonyloxy group (e.g. C_{1-6} alkyl-carbonyloxy such as acetyloxy, propionyloxy, etc.), a formylamino group, an amino group, a mono-lower alklylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dim thylamino, diethylamino,

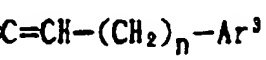
dipropylamino, dibutylamino, tc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.) or a lower alkyl-carbonylamino group (e.g. C_{1-6} alkyl-carbonylamino such as acetylamino, propionylamino, etc.) ("optionally halogenated lower alkyl," "optionally halogenated lower alkoxy" and "optionally halogenated lower alkylthio" have the same meanings as mentioned for the substituents of the "optionally substituted aromatic group" for Ar^3] (Preferred examples of Y include hydrogen atom, a hydroxyl group, a cyano group, a C_{1-6} alkoxy group, an amino group and a mono-C_{1-6} alkylamino group and, among them, a hydrogen group, a hydroxyl group, an amino group and a mono-C_{1-6} alkylamino group are preferred. Particularly preferred are a hydrogen atom and a hydroxyl group. A hydroxyl group is commonly used.)

[4] A group of the formula:



[wherein Ar^3 and n have the same meanings as defined above.], or

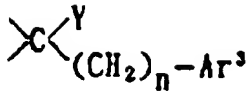
[5] A group of the formula:



[wherein Ar^3 and n have the same meanings as defined above.]

Preferred example of n is an integer of 0 to 2. More preferred is 0 or 1. Among them, 0 is particularly preferred.

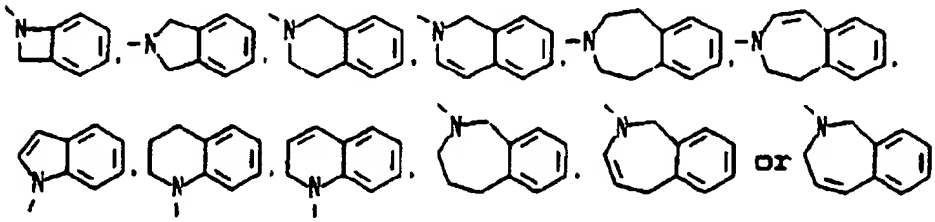
Among them, preferred example of Z include a group of the formula:



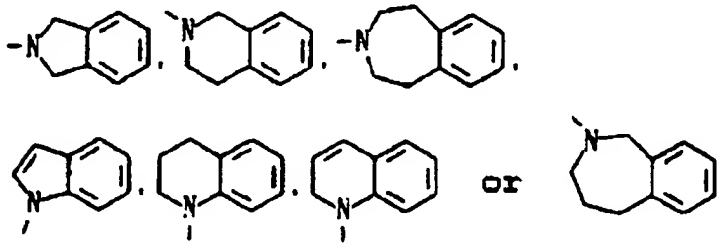
[wherein Ar^3 and n have the same meanings as defined above; and Y is a hydrogen atom or a hydroxyl group, preferably a hydroxyl group].

In the case that Z is a 1,2-phenylene group, examples of the ring represented by the formula:

include the following:

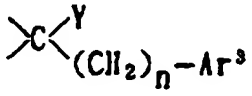


Among them,



is preferred.

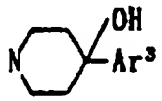
In the case that Z is a group represented by the formula:



[wherein Ar^3 and n have the same meanings as defined above; and Y is a hydrogen atom or a hydroxyl,

pref rably a hydroxyl group], th most preferred xamples of the ring represented by the formula:

include a group represented by the formula:



[wherein Ar^3 has the same meanings as defined above].

The substituent which may be present on the "1,2-phenylene" includes, for example, the same substituents as mentioned for the substituents of the "optionally substituted aromatic group". Preferred examples thereof include a halogen atom (particularly preferably fluorine, chlorine), a lower alkylendioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), a nitro group, a cyano group, an optionally halogenated lower alkyl group or an optionally halogenated lower alkoxy group.

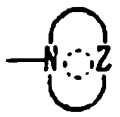
The "optionally halogenated lower alkyl group" and "optionally halogenated lower alkoxy group" include the same groups as mentioned for the substituents of the "optionally substituted aromatic group" for Ar^1, Ar^2 and Ar^3.

Preferred compound (I) or a salt thereof is one wherein Q^1 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_2CO-$;

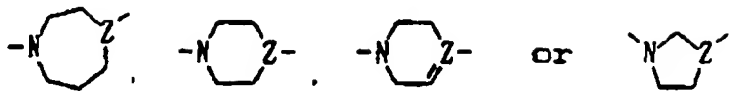
Q^2 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4$, $-CO-$, $-CH_2CO-$ or $-(CH_2)_2CO-$;

Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluoroph nyl, 2-pyridyl, 3-pyridyl or

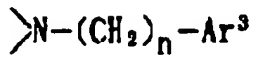
4-pyridyl;
a group of the formula:



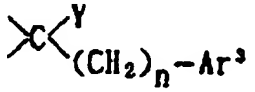
is



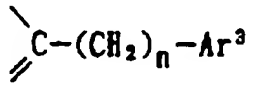
wherein Z is a group of the formula



[wherein Ar^3 is a C_{1-3} alkyl group optionally substituted with 1 to 3 halogen atoms, a C_{1-3} alkoxy group substituted with 1 to 3 halogen atoms or a phenyl group optionally substituted with a halogen atom (preferably chlorine, fluorine) (e.g. phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-dichlorophenyl, 3,5-difluorophenyl, 4-trifluoromethylphenyl, etc.), 2-pyridyl, 3-pyridyl or 4-pyridyl; and n is an integer of 0 to 3],



[wherein Ar^3 and n have the same meanings as defined above; and Y is a hydrogen atom, a hydroxyl group, an amino group or a mono-C_{1-6} alkylamino group (particularly a hydrogen atom and a hydroxyl group are preferred)] or



[wherein Ar^3 has the same meanings as defined abov];

R^1 is a hydrogen atom or methyl;

R^2 is (1) an C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group or a formyl group, or (2) an acyl group represented by $-(C=O)-R^4$, $-SO_2-R^4$, $-SO-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)O-R^4$;

R^3 is a hydrogen atom or a C_{1-3} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.; and

R^4 is a hydrogen atom, a lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), a lower alkenyl group (e.g. C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, etc.), a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, butyryl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a mono-lower alkylaminocarbonyl group (e.g. mono-C_{1-6} alkylaminocarbonyl such as methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, butylaminocarbonyl, etc.), a di-lower alkylaminocarbonyl group (e.g. di-C_{1-6} alkylaminocarbonyl such as dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, dibutylaminocarbonyl, etc.), a C_{6-10} aryl group (preferably phenyl) or a 5- to 7-membered cyclic amino group (preferably 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-pyrrolidinyl, 3-pyrrolidinyl, 2-piperazinyl, etc.).

The "lower alkyl group," "lower alkenyl group," "lower alkyl-carbonyl group," "carboxyl group," "lower alkoxy-carbonyl group," "mono-lower alkylaminocarbonyl group, "di-lower alkylaminocarbonyl group" and "5- to 7-membered cyclic amino group" for R^4 may have 1 to 3 substituents on any carbon atom. The substitu nt

includ , for exampl , (i) a halog n atom (e.g. fluorine, chlorine, bromine, iodine, tc.), (ii) a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), (iii) a nitro group, (iv) a cyano group, (v) a C_{1-6} alkyl group optionally substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (vi) a C_{3-6} cycloalkyl group, (vii) an optionally halogenated lower alkoxy group (e.g. optionally halogenated C_{1-6} alkoxy such as methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoromethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.), (viii) an optionally halogenated lower alkylthio group (e.g. optionally halogenated C_{1-6} alkylthio such as methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc.), (ix) a C_{7-16} aralkyl group, (x) a hydroxyl group, (xi)

an amino group, (xii) a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), (xiii) a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), (xiv) 5- to 7-membered cyclic amino group optionally having a hydroxyl group or an oxo group (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridone-1-yl, etc.), (xv) a lower alkyl-carbonyl group (C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xvi) a carboxyl group, (xvii) a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), (xviii) a formyl group which may be substituted with a 5- to 7-membered het rocyclic group having 1 to 3 het r atoms

s lected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group b ing optionally fused with a benzene ring, (xix) a carbamoyl group, (xx) a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.) whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group, (15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xxi) a di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.,) whose alkyl portion may be substituted with (1) a halogen atom, (2) a C_{1-3} alkylenedioxy group, (3) a nitro group, (4) a cyano group, (5) a C_{3-6} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (8) a hydroxyl group, (9) an amino group, (10) a mono-C_{1-6} alkylamino group, (11) a di-C_{1-6} alkylamino group, (12) a C_{1-6} alkyl-carbonyl group, (13) a carboxyl group, (14) a C_{1-6} alkoxy-carbonyl group,

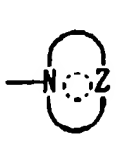
(15) a carbamoyl group, (16) a mono-C_{1-6} alkyl-carbamoyl group, (17) a di-C_{1-6} alkyl-carbamoyl group, (18) a C_{6-10} aryl-carbamoyl group, (19) a sulfo group, (20) a C_{1-6} alkylsulfonyl group, (21) a C_{6-10} aryl group, (22) a C_{6-10} aryloxy group or (23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (xxii) an aryl-carbamoyl group (e.g. C_{6-10} aryl-carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, etc.), (xxiii) a sulfo group, (xxiv) a lower alkylsulfonyl group (e.g. C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), (xxv) an aryl group (C_{6-10} aryl such as phenyl, naphthyl, etc.), (xxvi) an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.), (xxvii) a sulfamoyl group, (xxviii) a mono-lower alkyl-sulfamoyl group (e.g. C_{1-6} alkyl-sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, etc.), (xxix) a di-lower alkyl-sulfamoyl group (e.g. di-C_{1-6} alkyl-sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl, etc.), (xxx) a lower alkoxy-carbamoyl group (e.g. C_{1-6} alkoxy-carbamoyl such as methoxycarbamoyl, ethoxycarbamoyl, etc.), and (xxxi) a carbamoyloxy group.

More preferred is a compound wherein Q^1 is $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$;

Q^2 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CO-$ or $-(CH_2)_2CO-$;

Ar^1 and Ar^2 independently represent phenyl or 2-pyridyl;

a group of the formula:



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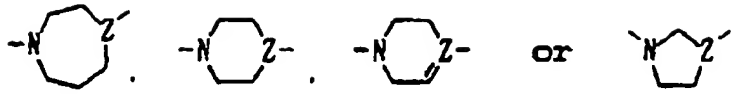
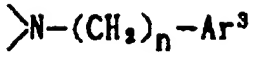
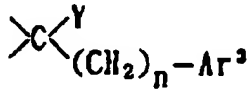


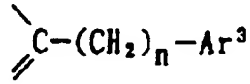
wherein Z is a group of the formula:



[wherein Ar^3 is a phenyl group optionally substituted with 1 to 3 (preferably 1 or 2) halogen atoms (preferably chlorine, fluorine) (e.g. phenyl, 4-chlorophenyl, 4-fluorophenyl, 3,5-dichlorophenyl, 3,5-difluorophenyl, etc.) or 2-pyridyl; and n represents 0];



[wherein Ar^3 and n have the same meanings as defined above; and Y is a hydrogen atom or a hydroxyl group] or



[wherein Ar^3 and n have the same meanings as defined above];

R^1 is a hydrogen atom or methyl;

R^2 is an acyl group represented by $-(C=O)-R^4$, $-(C=O)NR^5-R^4$ or $-(C=O)O-R^4$;

R^5 is a hydrogen atom; and

R^4 is a hydrogen atom, an optionally substituted lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as meth xycarbonyl, ethoxycarbonyl,

propoxycarbonyl, butoxycarbonyl, etc.), a phenyl group or 1-piperazinyl.

The "lower alkyl group" for R^4 may have 1 substituent on any carbon atom. The substituent include, for example, a hydroxyl group, an amino group, a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), a 5- to 7-membered cyclic amino group optionally having a hydroxyl group or an oxo group (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridone-1-yl, etc.), a lower alkyl-carbonyl group (C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a sulfamoyl group, a mono-lower alkyl-sulfamoyl group (e.g. mono-C_{1-6} alkyl-sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, etc.) or a di-lower alkyl-sulfamoyl group (e.g. di-C_{1-6} alkyl-sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl, etc.).

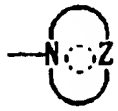
Particularly preferred is a compound wherein Q^1 is $-(CH_2)_3-$;

Q^2 is $-CH_2-$ or $-(CH_2)_2-$;

Ar^1 is a phenyl group or 2-pyridyl;

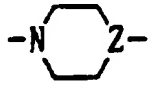
Ar^2 is a phenyl group;

a group of the formula:



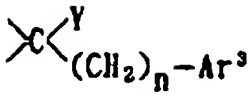
is

a group of the formula:



wherein Z is

a group of the formula:



[wherein Ar^3 is 4-chlorophenyl; n is 0; and Y is hydrogen atom or a hydroxyl group];

R^1 is a hydrogen atom;

R^2 is an acyl group represented by $-(C=O)-R^4$, $-(C=O)NR^5-R^4$ or $-(C=O)O-R^4$;

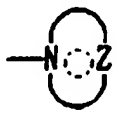
R^5 is a hydrogen atom; and

R^4 is a (1) hydrogen atom or (2) a lower alkyl group (C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) optionally having one substituent selected from (a) a hydroxyl group, (b) a 5- to 7-membered cyclic amino group optionally having (b-1) a hydroxyl group or (b-2) an oxo group (e.g. morpholino, piperzin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridon-1-yl, etc.) or (c) a sulfamoyl group.

In addition, preferred compound (I) is one wherein Ar^1 and Ar^2 independently represent, phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

Q^1 is a C_{1-4} alkylene group; Q^2 is a methylene group;

a group of the formula:



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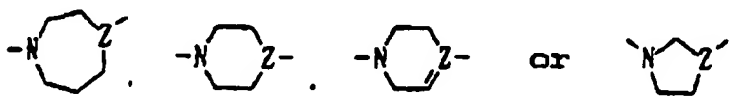
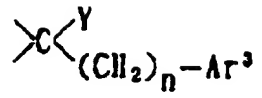


wherein Z is a group of the formula:



[wherein Ar^3 is a phenyl group optionally substituted with a halogen atom, n is an integer of 0 to 3, and Y is a hydrogen atom or a hydroxyl group];

R^1 is a hydrogen atom or methyl;

R^2 is (1) an alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group, a formyl group or (2) an acyl group represented by the formula:

$-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)O-R^4$

[wherein R^4 is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group which may have 1 to 5 substituents selected from (a) a hydroxyl group, (b) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (c) a mono-C_{1-6} alkylamino group, (d) a di-C_{1-6} alkylamino group, (e) a carboxyl group, (f) a C_{1-6} alkoxy-carbonyl group, (g) a mono-C_{1-6} alkyl-carbamoyl group, (h) a sulfo group which may be substituted with amino group (i) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (j) a C_{1-6} alkoxy-carbamoyl group, and (k) a carbamoyloxy group.

(iii) a C_{2-6} alkenyl group,

(iv) a C_{6-10} aryl group,

(v) a 5- to 11-membered heterocyclic group having at least one hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,

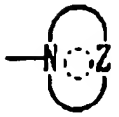
(vi) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkyl-carbonyl group,

(vii) a carboxyl group which may be substituted with a

C_{1-6} alkyl gr up,
(viii) a 5- to 7-membered cyclic amino group which may be substituted with
(a) a C_{1-6} alkyl group optionally substituted with (a-1) a hydroxyl group, (a-2) a di-C_{1-6} alkylamino group, (a-3) a C_{1-6} alkoxy-carbonyl group or (a-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(b) a C_{7-16} aralkyl group, (c) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (c-1) a halogen atom, (c-2) a mono-C_{1-6} alkylamino group, (c-3) a C_{1-6} alkoxy-carbonyl group or (c-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(d) a C_{1-6} alkoxy-carbonyl group, (e) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(f) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with a halogen atom or a C_{1-6} alkyl-carbonyl group, (g) an optionally halogenated C_{6-10} aryl-carbamoyl group, (h) an optionally halogenated C_{6-10} aryl-carbonyl group or (i) a C_{1-6} alkoxy-carbamoyl group, or
(ix) a C_{6-10} aryloxy group;
R^5 is a hydrogen atom or a C_{1-6} alkyl group].

More preferred compound (I) is one wherein Ar^1 and Ar^2 independently represent, phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

Q^1 is a C_{1-4} alkyl n group; Q^2 is a methylene group; a group of the formula:



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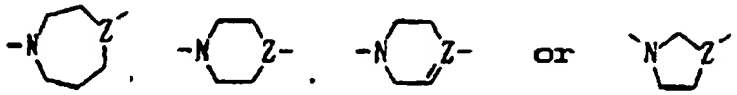
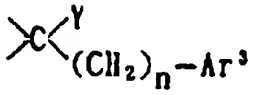


wherein Z is a group of the formula:



[wherein Ar^3 is a phenyl group optionally substituted with a halogen atom, n is an integer of 0 to 3, and Y is a hydrogen atom or a hydroxyl group];

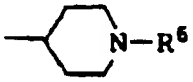
R^1 is a hydrogen atom or methyl;

R^2 is an acyl group represented by the formula:

$-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)O-R^4$

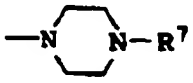
[wherein R^4 is represented by the formula:

(1)



or

(2)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with

(b-1) a hydroxyl group, (b-2) a di-C_{1-6} alkylamino group, (b-3) a C_{1-6} alkoxy-carbonyl group, or (b-4) a 5- to 7-member d heterocyclic group having 1 to 3 h tero

atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{7-16} aralkyl group, (d) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (d-1) a halogen atom, (d-2) a mono-C_{1-6} alkylamino group, (d-3) a C_{1-6} alkoxy-carbonyl group, or (d-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (e) a C_{1-6} alkoxy-carbonyl group, (f) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (g) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (g-1) a halogen atom, or (g-2) a C_{1-6} alkyl-carbonyl group, (h) an optionally halogenated C_{6-10} aryl-carbamoyl group, (i) an optionally halogenated C_{6-10} aryl-carbonyl group, or (j) a C_{6-10} aryloxy group; R^5 is a hydrogen atom or a C_{1-6} alkyl group].

Preferred compound (II) is one wherein Q^1 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_2CO-$;

Q^2 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CO-$, $-CH_2CO-$ or $-(CH_2)_2CO-$;

Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl or 4-pyridyl;

Ar^3 is (1) a phenyl optionally substituted with (a) a C_{1-3} alkyl group optionally substituted with 1 to 3 halogen atoms, (b) a C_{1-3} alkoxy group optionally substituted with 1 to 3 halogen atoms or (c) a halogen atom (preferably chlorine, fluorine) (e.g. phenyl, 4-chlorophenyl, 4-fluor phenyl, 4-methoxyph nyl,

3,5-dichlorophenyl, 3,5-difluorophenyl, 4-trifluoromethylphenyl, tc.), or (2) 2-pyridyl, 3-pyridyl or 4-pyridyl;

R^2 is an acyl group represented by $-(C=O)-R^4$, $-SO_2-R^4$, $-SO-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)O-R^4$;

R^5 is a hydrogen atom or a C_{1-3} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.; and

R^4 is (1) a hydrogen atom, (2) an optionally substituted lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), (3) an optionally substituted lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, butyryl, etc.), (4) a carboxyl group, (5) an optionally substituted lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), (6) an optionally substituted mono-lower alkylaminocarbonyl group (e.g. mono-C_{1-6} alkylaminocarbonyl such as methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, butylaminocarbonyl, etc.), (7) an optionally substituted a di-lower alkylaminocarbonyl group (e.g. di-C_{1-6} alkylaminocarbonyl such as dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, dibutylaminocarbonyl, etc.), (8) a C_{6-10} aryl group (preferably phenyl) or (9) an optionally substituted 5- to 7-membered cyclic amino group (preferably 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-pyrrolidinyl, 3-pyrrolidinyl, 2-piperazinyl, etc.).

The "lower alkyl group," "lower alkyl-carbonyl group," "lower alkoxy-carbonyl group," "mono-lower alkylaminocarbonyl group," "di-lower alkylaminocarbonyl" and "5- to 7-member d cyclic amino

group" for R^4 may have 1 to 3 substitu nts on any carbon atom. Th substitu nt include, for example, a (1) halogen group (e.g. fluorine, chlorine, bromine, iodine, etc.), (2) a lower alkylenedioxy group (e.g. C_{1-3} alkylenedioxy such as methylenedioxy, ethylenedioxy, etc.), (3) a nitro group, (4) a cyano group, (5) an optionally halogenated lower alkoxy group (e.g. optionally halogenated C_{1-6} alkoxy such as methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoromethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.), (6) an optionally halogenated lower alkylthio group (e.g. optionally halogenated C_{1-6} alkylthio such as methylthio, difluoromethylthio, trifluoromethylthion, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc.), (7) a hydroxyl group, (8) an amino group, (9) a mono-lower alkylamino group (e.g. mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), (10) a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), (11) a 5- to 7-membered cyclic amino group optionally having a hydroxyl group or an oxo group (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridone-1-yl, etc.), (12) an acylamino group ("acylamino group" include, for example, the same groups as mentioned for the substituents of the "optionally substituted aromatic group" for Ar^1, Ar^2 and Ar^3 and preferred examples thereof include $-NHCOOR^3$, $-NHCONHR^3$ and $-NHCOR^3$ (R^3 is a lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) or a lower

alkoxy group (e.g. C_{1-6} alkoxy such as methoxy, thoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.)), (13) a lower alkyl-carbonyl group (e.g. C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), (14) a carboxyl group, (15) a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), (16) a carbamoyl group, (17) a mono-lower alkyl-carbamoyl group (e.g. mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc.), (18) a di-lower alkyl-carbamoyl group (e.g. di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc.), (19) an aryl-carbamoyl group (e.g. C_{6-10} aryl-carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, etc.), (20) a sulfo group, (21) a lower alkylsulfonyl group (e.g. C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), (22) an aryl group (C_{6-10} aryl such as phenyl, naphthyl, etc.), (23) an aryloxy group (e.g. C_{6-10} aryloxy such as phenyloxy, naphthyloxy, etc.), (24) a sulfamoyl group, (25) a mono-lower alkyl-sulfamoyl group (e.g. mono-C_{1-6} alkyl-sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, etc.) or (26) a di-lower alkyl-sulfamoyl group (e.g. di-C_{1-6} alkyl-sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl, etc.).

More preferred is a compound wherein Q^1 is $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$;

Q^2 is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CO-$ or $-(CH_2)_2CO-$;

Ar^1 and Ar^2 independently represent phenyl or 2-pyridyl;

Ar^3 is a phenyl group optionally substituted with 1 to 3 halogen atoms (preferably chlorine, fluorine) (e.g. phenyl, 4-chlorophenyl, 4-fluorophenyl, 3,5-dichlor ph nyl, 3,5-difluoroph nyl, etc.) or

2-pyridyl;

R^2 is (1) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group or a formyl group, or (2) an acyl group represented by $-(C=O)-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)O-R^4$;

R^5 is an hydrogen atom; and

R^4 is a hydrogen atom, an optionally substituted lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), a carboxyl group, a lower alkenyl group (e.g. C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, etc.), a lower alkoxy-carbonyl group (e.g. C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a phenyl group or 1-piperazinyl.

The "lower alkyl group" for R^4 may have 1 to 3 substituents on any carbon atom. The substituent include, for example, a hydroxyl group, an amino group, a di-lower alkylamino group (e.g. di-C_{1-6} alkylamino such as dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.), a 5- to 7-membered cyclic amino group optionally having a hydroxyl group or an oxo group (e.g. morpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridone-1-yl, etc.), an acylamino group ("acylamino group" include $-NHCOOR^3$, $-NHCONHR^3$ and $-NHCOR^3$ (R^3 is a lower alkyl group (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) or a lower alkoxy group (e.g. C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.)), a lower alkyl-carbonyl group (C_{1-6} alkyl-carbonyl such as acetyl, propionyl, etc.), a carboxyl group, a lower alkoxy-carbonyl group (.g. C_{1-6} alkoxy-carbonyl such as

m thoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tc.), a sulfamoyl group, a mono-lower alkyl-sulfamoyl group (e.g. mono-C_{1-6} alkyl-sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, etc.) or a di-lower alkyl-sulfamoyl group (e.g. di-C_{1-6} alkyl-sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl, etc.).

Particularly preferred is a compound wherein Q^1 is $-(CH_2)_3-$;

Q^2 is $-CH_2-$ or $-(CH_2)_2-$;

Ar^1 is phenyl or 2-pyridyl;

Ar^2 is phenyl;

Ar^3 is 4-chlorophenyl; n is 0; and Y is an hydrogen atom or a hydroxyl group];

R^2 is an acyl group represented by $-(C=O)-R^4$, $-(C=O)NR^5-R^4$ or $-(C=O)O-R^4$;

R^5 is a hydrogen atom; and

R^4 is (1) a hydrogen atom or (2) a lower alkyl group (C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) an optionally having one substituent selected from a (a) hydroxyl group, (b) a 5- to 7-membered cyclic amino group optionally having a hydroxyl group or an oxo group (e.g. morpholino, piperzin-1-yl, piperidino, pyrrolidin-1-yl, 2-pyrrolidon-1-yl, 2-pyridon-1-yl, etc.) and (c) a sulfamoyl group.

In addition, preferred Compound (II) is one wherein Ar^1 and Ar^2 independently represent, phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

Q^1 is a C_{1-4} alkylene group; Q^2 is a methylene group;

R^2 is (1) an alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group, a formyl group or (2) an acyl

group represented by the formula:

$-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)O-R^4$

[wherein R^4 is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group which may have 1 to 5 substituents selected from (a) a hydroxyl group, (b) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (c) a mono-C_{1-6} alkylamino group, (d) a di-C_{1-6} alkylamino group, (e) a carboxyl group, (f) a C_{1-6} alkoxy-carbonyl group, (g) a mono-C_{1-6} alkyl-carbamoyl group, (h) a sulfo group which may be substituted with amino group (i) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (j) a C_{1-6} alkoxy-carbamoyl group, and (k) a carbamoyloxy group.

(iii) a C_{2-6} alkenyl group,

(iv) a C_{6-10} aryl group,

(v) a 5- to 11-membered heterocyclic groups having at least one hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,

(vi) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkyl-carbonyl group,

(vii) a carboxyl group which may be substituted with a C_{1-6} alkyl group,

(viii) a 5- to 7-membered cyclic amino group which may be substituted with

(a) a C_{1-6} alkyl group optionally substituted with (a-1) a hydroxyl group, (a-2) a di-C_{1-6} alkylamino group, (a-3) a C_{1-6} alkoxy-carbonyl group or (a-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

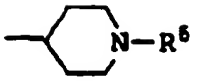
(b) a C_{7-16} aralkyl group, (c) a C_{1-6} alkyl-carbonyl group whos alkyl portion may be substitut d with (c-1) a halogen atom, (c-2) a mono-C_{1-6} alkylamino group, (c-3) a C_{1-6} alkoxy-carbonyl group or (c-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(d) a C_{1-6} alkoxy-carbonyl group, (e) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(f) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with a halogen atom or a C_{1-6} alkyl-carbonyl group, (g) an optionally halogenated C_{6-10} aryl-carbamoyl group, (h) an optionally halogenated C_{6-10} aryl-carbonyl group or (i) a C_{1-6} alkoxy-carbamoyl group, or
(ix) a C_{6-10} aryloxy group;
R^5 is a hydrogen atom or a C_{1-6} alkyl group]; and
Ar^3 is a phenyl group optionally substituted with a halogen atom.

In addition, preferred Compound (II) is one wherein Ar^1 and Ar^2 independently represent, phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;
Q^1 is a C_{1-4} alkylene group; Q^2 is a methylene group;
R^2 is (1) an alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group, a formyl group or (2) an acyl group represented by the formula:

$$-(C=O)-R^4,\ -SO_2-R^4,\ -(C=O)NR^5-R^4 \text{ or } -(C=O)O-R^4$$

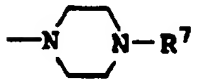
[wher in R^4 is a group represented by the formula:

(1)



or

(2)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with (b-1) a hydroxyl group, (b-2) a di-C_{1-6} alkylamino group, (b-3) a C_{1-6} alkoxy-carbonyl group, or (b-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{7-16} aralkyl group, (d) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (d-1) a halogen atom, (d-2) a mono-C_{1-6} alkylamino group, (d-3) a C_{1-6} alkoxy-carbonyl group, or (d-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (e) a C_{1-6} alkoxy-carbonyl group, (f) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (g) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (g-1) a halogen atom, or (g-2) a C_{1-6} alkyl-carbonyl group, (h) an optionally halogenated C_{6-10} aryl-carbamoyl group, (i) an optionally halogenated C_{6-10} aryl-carbonyl group, or (j) a C_{6-10} aryloxy group;

and
R^5 is a hydrogen atom or a C_{1-6} alkyl group]; and
Ar^3 is a phenyl group optionally substituted with a halogen atom.

Examples of the preferred compound include the following.
5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1-formylamino-2,2-diphenylpentane hydrochloride,
5-[4-(4-Fluorophenyl)-piperadin-1-yl]-1-formylamino-2,2-diphenylpentane dihydrochloride,
7-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1-formylamino-2,2-diphenylheptane hydrochloride,
1-[5-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-hydroxypropyl)urea hydrochloride,
1-[5-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(4-hydroxybutyl)urea hydrochloride,
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-diethylaminopropyl)urea,
2-[3-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]ureido]ethanesulfonamide hydrochloride,
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenyl]pentylmalonamic acid,
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenyl]pentylglutamic acid,
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2-phenyl-(2-pyridyl)]pentylsuccinamic acid,
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino}-2,2-diphenylpentyl]-3-(piperidin-4-yl)urea,
Ethyl 4-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino] piperidino-4-oxobutyrate,
N-Ethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino-1-piperidinecarboxamide,
N-Ethoxycarbonylmethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylp ntyl]aminocarbonyl-

amino-1-piperidinecarboxamide,
Ethyl 3-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino piperidino]-3-oxopropionate,
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(1-ethylpiperidin-4-yl)urea,
1-[(Piperidin-4-yl)carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[(N-Ethylcarbamoyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[N-(Ethoxycarbonylacetyl)piperidin-4-yl]carboamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[N-(3-Methoxycarbonylpropionyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane, or a salt thereof.

Among them, especially,
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(piperidin-4-yl)urea,
Ethyl 4-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino] piperidino-4-oxobutyrate,
N-Ethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino-1-piperidinecarboxamide,
N-Ethoxycarbonylmethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]aminocarbonyl-amino-1-piperidinecarboxamide,
Ethyl 3-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentylaminocarbonylamino] piperidino]-3-oxopropionate,
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(1-ethylpiperidin-4-yl)urea,
1-[(Piperidin-4-yl)carboamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,

1-[[(N-Ethylcarbamoyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,

1-[[N-(Ethoxycarbonylacetyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,

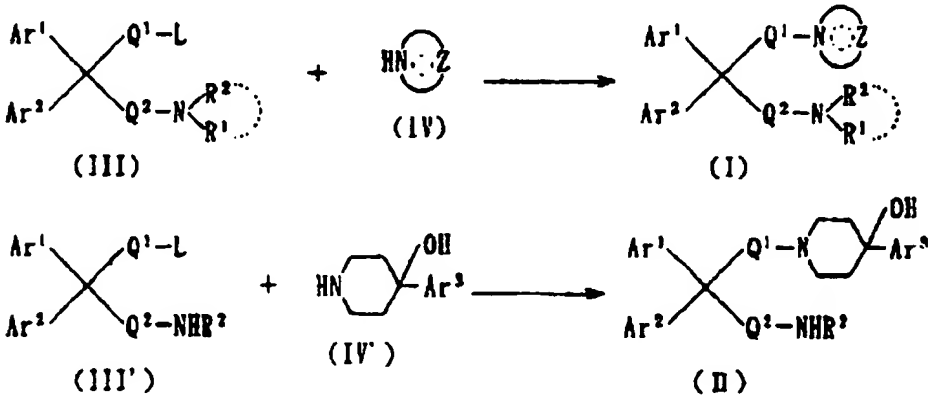
1-[[N-(3-Methoxycarbonylpropionyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane or a salt thereof, is preferred.

The above mentioned compounds may be in any form of free compound, salt, hydrate, etc.

While a plurality of synthetic technologies are contemplatable for producing the compound (I) and a salt thereof (hereinafter abbreviated to a "compound (I)," merely) and compound (II) and a salt thereof (hereinafter abbreviated to a "compound (II)," merely), typical production technology will be illustrated as follows:

In the explanation of the following processes, starting materials and reaction products may form a salt thereof which does not inhibit the reaction.

Process 1



(In the above schema, L is a leaving group and the other symbols have the same meanings as defined above).

The reaction is carried out applying a usual

alkylation of an amino group [e.g. procedure described in Organic Functional Group Preparations, Vol. 2, Academic Press Inc.]. Examples of the leaving group include a halogen atom (preferably chloro, bromo, iodo, etc.), a methanesulfonyloxy group, a p-toluenesulfonyloxy group, a benzenesulfonyloxy group, etc.

The reaction is carried out by stirring in an inert solvent within the range from room temperature to 100°C (preferably room temperature to 50°C) for 0.5 to 1 day. Usually, 1 to 3 equivalents of a base is added to the reaction system but is not essential. As the inert solvent, alcoholic solvent, etheral solvent, halogenated solvent, aromatic solvent, acetonitrile, N,N-dimethylformylamido (DMF), acetone, methyl ethyl ketone and dimethyl sulfoxide can be used alone or in combination thereof. Among them, acetonitrile, DMF, acetone and ethanol are preferred.

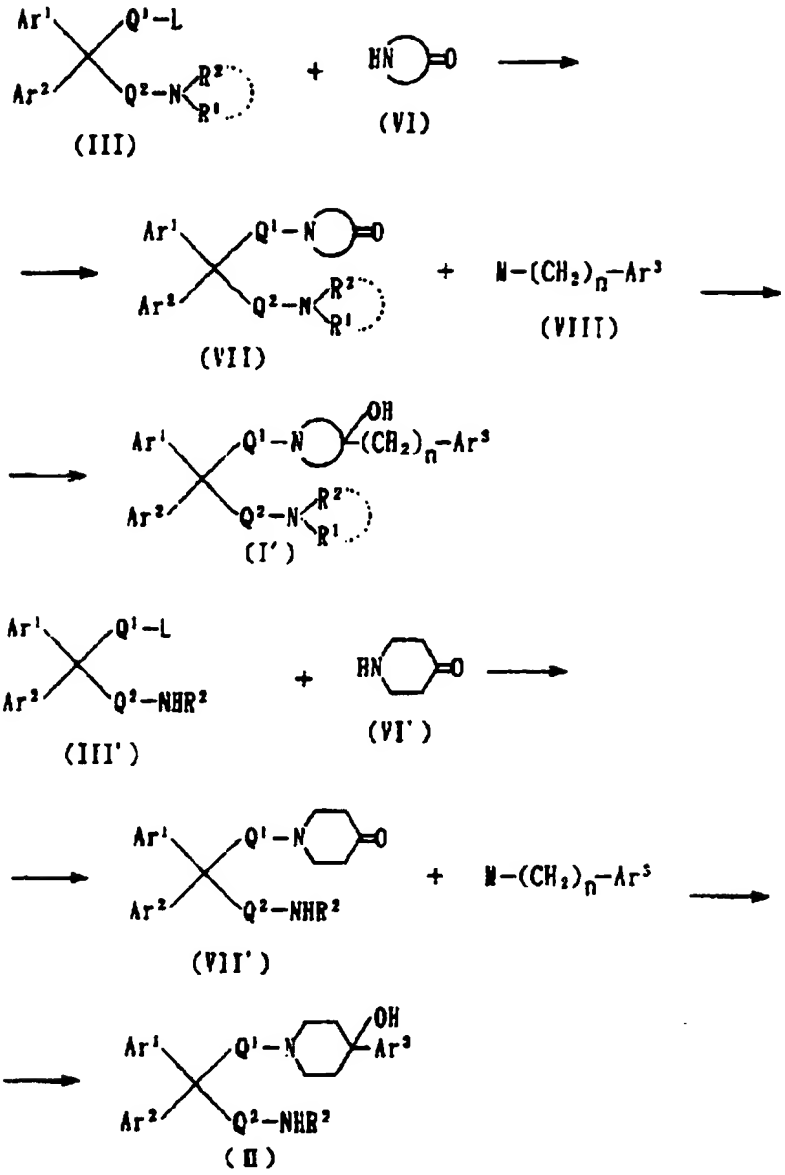
The base include strong bases (1) such as hydrides of alkaline or alkaline earth metals (e.g. lithium hydride, sodium hydride, potassium hydride, calcium hydride, etc.), amides of alkaline or alkaline earth metals (e.g. lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethylsilazide, sodium hexamethylsilazide, potassium hexamethylsilazide, etc.) and lower (C_{1-4}) alkoxides of alkaline or alkaline earth metals (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.); inorganic salts (2) such as hydroxides of alkaline or alkaline earth metals (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, etc.), carbonates of alkaline or alkaline earth metals (e.g. sodium carbonate, potassium carbonate, cesium carbonate, etc.) and hydrogencarbonates of alkaline or alkaline earth metals (e.g. sodium hydrog ncarbonate, potassium

hydrogencarbonate, etc.); and organic bases (3) such as amines (.g. triethylamine, diisopropylethylamine, N-methylmorpholine, 4-dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]-7-undecene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), etc.) and basic heterocyclic compounds (e.g. pydridine, imidazole, 2,6-lutidine, etc.).

The compound (I) or (II) obtained by the above process can be further converted to the objective product of this invention by a usual organic synthesis reaction such as hydrolysis, halogenation, oxidation, reduction, alkylation, acylation, ring formation etc. The reaction examples include the following process.

When the compound has carbonyl in the molecule, it can be converted to the following compound having a hydroxyl group by the Grignard reaction.

Process 2



(wherein M is a metal (e.g. lithium, sodium, bromomagnesium, etc.) used for so-called Grignard reaction; and the other symbols have the same meanings as defined above).

The Grignard reaction is conducted by r acting 1

to 10 equivalents of a so-called Grignard reagent prepared separat ly or alkyl lithium or alkyl sodium with the compound (VII) or (VII') in an etheral solvent at room temperature to 80°C (preferably 30 to 60°C) for 1 to 24 hours. The reaction is preferably conducted under the condition of deoxidation in the absence of water. It is preferred to conduct the reaction in the presence of anhydrous cerium chloride (catalytic amount to 2 equivalent, preferably 1 equivalent).

When R^1 and R^2 independently represent an acyl group or an alkyl-carbonyl group, the group can be converted into an alkyl group by the reduction.

The reduction can be conducted by the procedure using metal hydrides or catalytic reduction process. The catalytic reduction process can be conducted by reacting with a catalytic amount of a metal catalyst such as Raney-nickel, platinum oxide, palladium metal, palladium-on-carbon, etc. in an inert solvent (e.g. alcoholic solvent) at room temperature to 100°C under a hydrogen pressure of 1 to 100 atm for 1 to 48 hours.

The reduction using the metal hydride can be easily conducted in an inert solvent using a metal hydride (e.g. lithium aluminum hydride, sodium borohydride, lithium borohydride, sodium cyanoborohydride, diborane, dibutylaluminum hydride, etc.) or a metal (e.g. zinc, iron, sodium, potassium, etc.). The inert solvent include etheral solvents (e.g. diethyl ether, tetrahydrofuran, dioxane, etc.), alcoholic solvents (e.g. methanol, ethanol, tert-butanol, etc.), toluene and hexane. The preferred metal hydride include lithium aluminum hydride. The amount of the metal hydride to be used is from 4 to 20 equivalents, more preferably from 6 to 12 equivalents. The reaction is conducted at the reaction temperature of -70 to 100°C for 30 minutes to 18 hours. The pref rred reaction temperature varies dep nding on the

kind of a r ducing agent to be used, but is usually from 30 to 70°C. It is also possible to selectively reduce only a cyano or ester group.

The conversion from a ketone represented by the compound (VII) or (VII') to an alcohol of -CH(OH) can be easily accomplished by reacting with the metal hydride (e.g. lithium aluminum hydride, sodium borohydride, lithium borohydride, sodium cyanoborohydride, diborane, dibutylaluminum hydride, etc.) in an inert solvent. The inert solvent include etheral solvents (e.g. ethyl ether, tetrahydrofura, dioxane, etc.) and alcoholic solvents (e.g. methanol, ethanol, tert-butanol, etc), toluene and hexane. The amount of the metal hydride to be used is from 1 to 20 equivalents, more preferably from 3 to 12 equivalents. The reaction temperature is from -70 to 100°C. The preferred reaction temperature and reaction time vary depending on the kind of a reducing agent to be used. In case of the metal hydride, the reduction is preferably conducted at 0 to 30°C for 30 minutes to 18 hours.

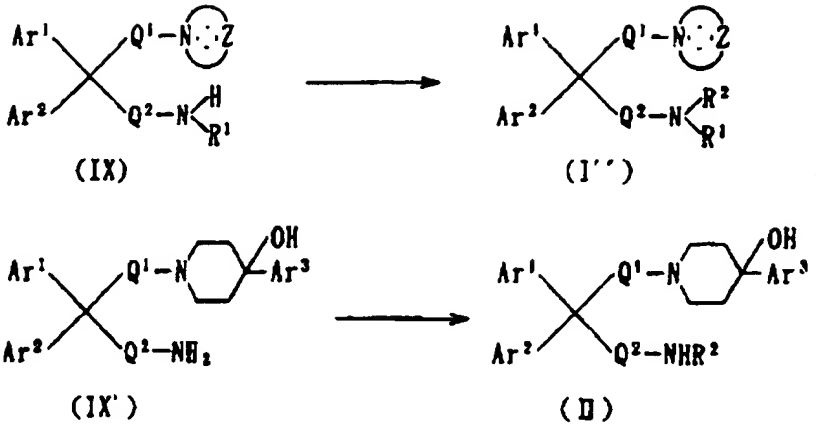
When R^1 or R^2 independently represents an acyl group, the group can also be converted into another acyl group, directly or through hydrolysis. The hydrolysis includes an alkali hydrolysis and an acid hydrolysis. In case of the "alkali hydrolysis," a compound is reacted with an alkali (e.g. inorganic hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, etc.) in a solvent (e.g. water, alcohols, ethers alone or a mixed solvent using two or more kinds of them). As the solvent, a mixed solvent of water and methanol is preferred. As the alkali, sodium hydroxide is preferred. The usage amount of the alkali is about 2 to 100 equivalents, preferably about 5 to 100 equival nts, relative to the compound. The reaction

temperature is from about 10 to 120°C, pr ferably from about 50 to 120°C. The reaction time is from about 5 minutes to 100 hours, preferably from about 10 to 50 hours. In the preferred reaction example, the solvent is a mixed solvent of water and methanol and the reaction temperature is from about 50 to 120°C and, th reaction time is from about 10 to 50 hours.

Regarding the "acid hydrolysis process," a compound may be heated with stirring in water, acetic acid or an alcoholic solvent in the presence of an excess amount of mineral acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, etc.) at room temperature to 120°C for 0.5 to 18 hours. Preferably, the heating is conducted in the presence of dilute hydrochloric acid alone or in combination with acetic acid at room temperature to 60°C.

When R^1 and R^2 independently represent a "protective group of an amino group," there can be sometimes used reduction process, ultraviolet irradiation process, hydrazine process, etc. in addition to the hydrolysis process. Typical examples of the "reduction process" include a catalytic reduction process. For example, starting materials are stirred in an inert solvent (e.g. water, alcoholic solvent, ethyl acetate, etheral solvent, etc.) in the presence of metal catalysts (catalytic amount to one equivalent) such as palladium catalyst (e.g. palladium acetate, palladium-carbon, palladium black, palladium-barium carbonate, etc.), platinum oxide and Ranney-nickel, etc. at room temperature to 100°C under a hydrogen pressure of 1 to 100 atm (preferably from 1 to 10 atm) for 0.5 to 24 hours. If necessary, a catalytic amount to 2 equivalents of a mineral acid such as hydrochloric acid or an organic acid such as acetic acid is sometimes added.

Proc ss 3



(IX) (I'') (IX') (II)

[In the above schema, R^2 is an acyl group; and the other symbols have the same meanings as defined above].

The acylation can be conducted according to the per se known procedure described in Organic Functional Group Preparations, Vol. 2, Academic Press Inc.

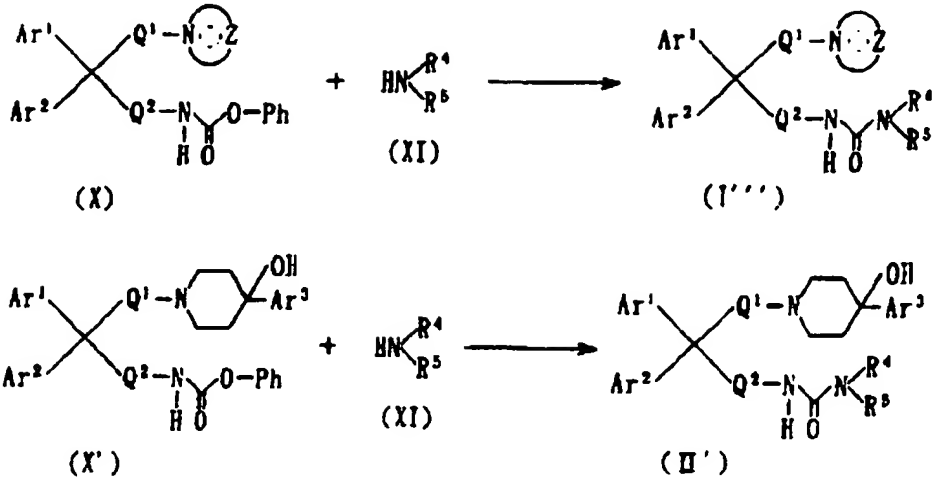
For example, when an acyl group represented by R^7 is $-(C=O)-R^4$, $-SO_2-R^4$, $-SO-R^4$ or $-(C=O)O-R^4$ (R^4 is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group), the acylation reaction is conducted by reacting 1 to 5 equivalents, preferably 1 to 3 equivalents, of a reactive derivative of the corresponding organic acid with the compound (IX) or (IX') in an inert solvent at the reaction temperature of -20 to 50°C (preferably 0°C to room temperature) for 5 minutes to 100 hours. As the inert solvent, there can be used etheral solvent, halogenated solvent, aromatic solvent, acetonitrile, N,N-dimethylformulamido (DMF), acetone, methyl ethyl ketone, dimethylsulfoxide (DMSO), water, etc. alone or in combination thereof. Among them, acetonitrile, dichloromethane and chloroform are preferred. The reaction sometimes proceed more smoothly in the presence of 1 to 10 equivalents, preferably 1 to 3 equivalents of a base. As the base, both inorganic and organic bases are effective. The inorganic base

includes hydroxides, hydrides, carbonates, hydrogencarbonat s, organic acid salts of alkaline or alkaline earth metals. Among them, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate and potassium hydrogencarbonate are preferred. As the organic base, tertiary amines such as triethylamine is preferred. The reactive derivative includes acid anhydride, acid halide (e.g. acid chloride, acid bromide, etc.) and active ester. Among them, acid halide is preferred.

Acylation using carboxylic acid can be used a procedure of reacting 1 to 1.5 equivalents of carboxylic acid in an inert solvent (e.g. halogenated solvent, acetonitrile, etc.) with a dehydration condensing agent such as dicyclohexylcarbodiimide (DCC) (1 to 1.5 equivalents) at room temperature for 0.5 to 24 hours.

When an acyl group represented by R^2 is $-(C=O)NH-R^4$, $-(C=S)NH-R^4$, $-(C=S)O-R^4$ or $-(C=O)O-R^4$ (R^4 has the same meanings as defined above), the acylation is conducted in an inert solvent (e.g. halogenated solvent, acetonitrile, etc.) at the reaction temperature of -20 to 50°C (preferably 0°C to room temperature) for 5 minutes to 100 hours, using one equivalent or excess amount of the corresponding isocyanate ($OCN-R^4$ (R^4 has the same meanings as defined above) and isothiocyanate ($SCN-R^4$ (R^4 has the same meanings as defined above). In order to accelarate the reaction, the reaction is sometimes conducted in the presence of 1 to 10 equivalents of an organic base such as triethylamine. When the acyl group represented by R^2 is $-CONR^5-R^4$ (R^4 and R^5 have the same meanings as defined above) (hydrogen is preferred as R^5), it is also possible to produc by the following xchange reaction (process 4).

Process 4



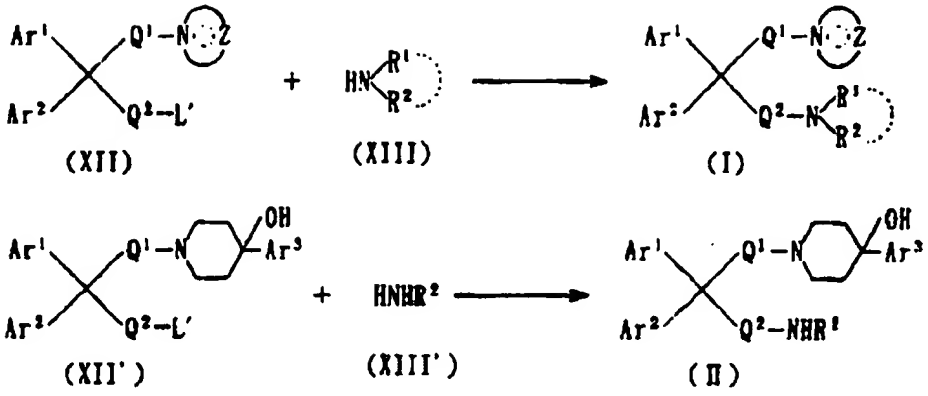
(X) (XI) (I''')

(X') (XI) (II')

[wherein Ph is a phenyl group; and the other symbols have the same meanings as defined above].

The reaction proceeds by reacting one equivalent to excess amount of amine ($HN-R^4-R^5$ (R^4 and R^5 have the same meanings as defined above)) with the compound (X) or (X') in an inert solvent such as acetonitrile, DMF, water, etc. in the presence of 1 to 10 equivalents of an inorganic base (e.g. potassium carbonate, sodium carbonate, etc.) at room temperature to 50°C for 1 to 24 hours.

Process 5



(XII) (XIII) (I)

(XII') (XIII') (II)

[wherein, the symbols have the same meanings as defined above; and L' is a leaving group].

In the process 5, the objective product can be obtained by reacting 1 equivalent to excess amount of:

 (XIII) or $HNHR^2$ (XIII')

with the compound (XII) or (XII'). The reaction conditions are the same as those of the alkylation reaction of the amino group in the "process 1." As the base, the above strong base, inorganic base or organic base is used.

The leaving group L' used in the "process 5" includes the same one for L. Among them, bromo and iodo are preferred. When "R^1 and R^2 bonds together with the adjacent nitrogen to form an optionally substituted nitrogen-containing heterocyclic group," the objective product can be synthesized by introducing the corresponding nitrogen-containing heterocycle according to the "process 5." For example, morpholino, piperazino, 1-piperazinyl, 1-imidazolyl, phthalimide, etc. can be easily introduced.

The compound used as the starting material in the above "process 1" and "process 2" can be synthesized by

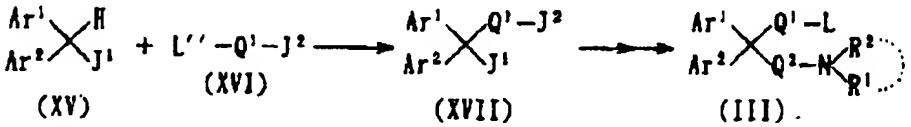
using the synth sis procedures which are known in r f renc s in combination. For xample, the following compound used in the above "process 1" is easily available or synthesized.

(XIV)

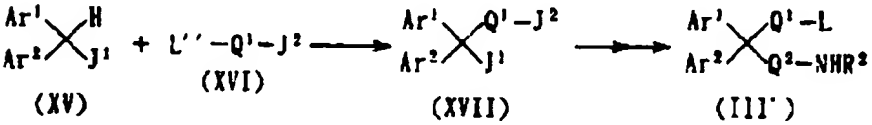
Among them, the compound wherein Z is $-C(OH)-(CH_2)n-Ar^3$ can be produced from the corresponding ketone according to the same manner as that described in "process 2."

The compound (III) or (III') as the starting material can be synthesized by the per se known procedure, and examples thereof include the following schema 1.

Schema 1



(XV) (XVI) (XVII) (III).



(XV) (XVI) (XVII) (III')

[wherein J^1 is a cyano group, a carboxyl group, a lower (C_{1-3}) alkoxy-carbonyl group or a formyl group; J^2 is a group capable of converting into a leaving group (e.g. cyano, carboxyl, lower (C_{1-3}) alkoxy-carbonyl, protected hydroxyl group, etc.); L" is the same meanings as defined in L; and the other symbols have the same meanings as defined above.]

It is possible to convert to the compound (XVII) by reacting the compound (XV) with one equivalent to excess amount of the compound (XVI) in any inert solvent (e.g. etheral solv nt, DMF, DMSO, alcoholic

solvent, acetonitrile, ac tone, tc.) or mixed solvent thereof in th presenc of a bas (usually 1 to 3 equivalents) at -20 to 120°C for 5 minutes to 24 hours. The compound (XVII) can also be obtained by heating the compound (XV) and excess acrylonitrile or lower alkyl acrylate (2 to 10 equivalents) in the presence of a base catalyst.

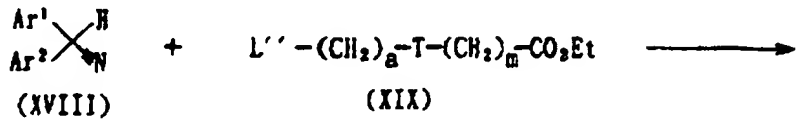
The base include strong bases (1) such as hydrides of alkaline or alkaline earth metals (e.g. lithium hydride, sodium hydride, potassium hydride, calcium hydride, etc.), amides of alkaline or alkaline earth metals (e.g. lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethylsilazide, sodium hexamethylsilazide, potassium hexamethylsilazide, etc.) and lower (C_{1-4}) alkoxides of alkaline or alkaline earth metals (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.); inorganic salts (2) such as hydroxides of alkaline or alkaline earth metals (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, etc.), carbonates of alkaline or alkaline earth metals (e.g. sodium carbonate, potassium carbonate, cesium carbonate, etc.) and hydrogencarbonates of alkaline or alkaline earth metals (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, etc.); and organic bases (3) such as amines (e.g. triethylamine, diisopropylethylamine, N-methylmorpholine, 4-dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]-7-undecene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), etc.) and basic heterocyclic compounds (e.g. pyridine, imidazol, 2,6-lutidine, etc.).

The compound (XVII) can be converted to the compound (III) or (III') by appropriately combining per se known processes, for example, general organic synthesis r actions such as hydrolysis, halogenation,

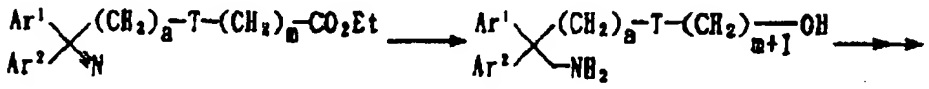
oxidation, reduction, alkylation, acylati n, ring formation etc.

The reaction example include the following process.

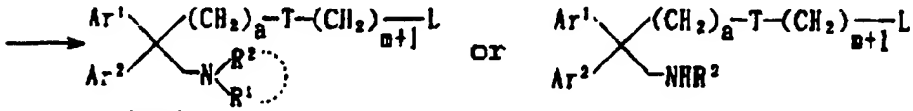
Method 1



(XVIII) (XIX)

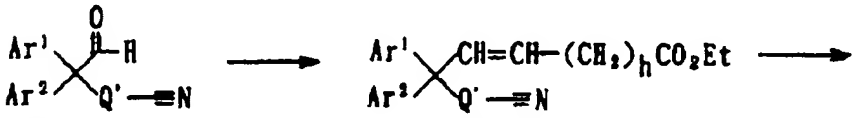


(XX) (XXI)

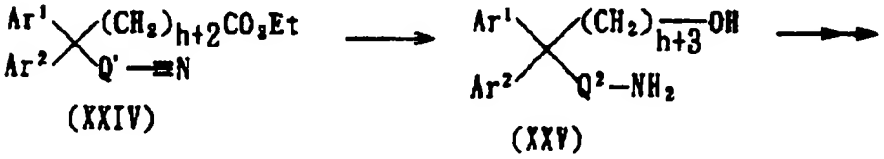


(III) (III')

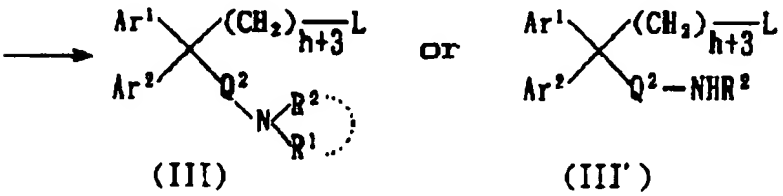
Method 2



(XXII) (XXIII)



(XXIV) (XXV)



(III) (III')

[wh rein T is a bond, an oxygen atom or an

optionally oxidiz d sulfur atom; L and L" ind pendently represent a leaving group; a and m independently represent an integer of 0 to 5 and the total of them is 1 to 6; h is an integer of 0 to 2; and Q' is a group obtained by removing one methylene group from Q^2.]

The reduction reaction of the compound (XX) and the compound (XXIV) can be conducted by the process using metal hydrides or catalytic reduction process. The catalytic reduction process can be conducted by reacting with a catalytic amount of a metal catalyst such as Ranney-nickel, platinum oxide, metallic palladium, palladium-carbon, etc. in an inert solvent (e.g. alcoholic solvent) at room temperature to 100°C under a hydrogen pressure of 1 to 100 atm for 1 to 48 hours.

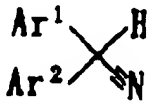
The reduction reaction using the metal hydride can be easily conducted by reacting in an inert solvent using a metal hydride (e.g. lithium aluminum hydride, sodium borohydride, lithium borohydride, sodium cyanoborohydride, diborane, dibutylaluminum hydride, etc.) or a metal (e.g. zinc, iron, sodium, potassium, etc.). The inert solvent include etheral solvents (e.g. dyiethyl ether, tetrahydrofuran, dioxane, etc.), alcoholic solvents (e.g. methanol, ethanol, tert-butanol, etc.), toluene and hexane. The preferred metal hydride include lithium aluminum hydride. The amount of the metal hydride to be used is from 4 to 20 equivalents, more preferably from 6 to 12 equivalents. The reaction temperature is from -70 to 100°C. The preferred reaction temperature varies depending on the kind of a reducing agent to be used, but is normally from 30 to 70°C. The reaction time is from 30 minutes to 18 hours. It is also possible to selectively reduce only a cyano or ester group.

The conversion from a hydroxyl group to a leaving group or introduction of a protective group of an amino

group can be c nducted according to the procedure described in Comprehensive Organic Transformations, VCH Publishers Inc.

The compound (XXII) can be converted to the compound (XXIII) by the Wittig reaction. The reaction can be conducted in an inert solvent (e.g. alcoholic solvent, etheral solvent, etc.), if necessary, in the presence of a base at 20 to 60°C for 5 minutes to 18 hours, using 1 equivalent to excess amount of a Witting reagent (e.g. ethyl triphenylphosphoranilidene-acetate, ethyl diethylphosphonoacetate, etc.). The base include strong bases (1) such as sodium hydride, t-butoxy potassium, etc.); inorganic bases (2) such as hydroxides of alkaline or alkaline earth metals (e.g. sodium hydride, potassium hydroxide, lithium hydroxide, barium hydroxide, etc.), carbonates of alkaline or alkaline earth metals (e.g. sodium carbonate, potassium carbonate, cesium carbonate, etc.) and hydrogencarbonates of alkaline or alkaline earth metals (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, etc.); and organic bases (3) amines (e.g. triethylamine, DBU, etc.).

In case of reducing the double bond, the catalytic reduction process mentioned above can be used.



(XVIII)

as one of starting materials can be synthesized from aryl acetonitrile or diaryl ketone according to the per se known procedure (e.g. Synthesis, page 172, 1977).

Moreover, in any of the aforementioned reactions and any of the reactions for synthesizing the starting compounds, when the raw materials have amino, carboxyl or hydroxyl group as a substituent, these functional

groups may be protected with protectiv groups which are commonly used in peptide chemistry or related art. The desired compounds can be then be obtained by eliminating such protective groups when needed.

The amino-protective group that can be used includes, for example, C_{1-6} alkyl-carbonyl (e.g. formyl, acetyl, ethylcarbonyl, etc.), C_{1-6} alkyloxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.), benzoyl group, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), trityl, phthaloyl and N,N-dimethylaminomethylene. These groups may respectively have 1 to 3 substituents, for example, halogen (e.g. fluorine, chlorine, bromine, iodine, etc.) and nitro.

The carboxyl-protective group which can be used includes, for example, C_{1-6} alkyl (e.g. methyl, ethyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl and silyl. These groups may respectively have 1 to 3 substitutes, for example, halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl-carbonyl (e.g. formyl, acetyl, propionyl, butylcarbonyl, etc.) and nitro.

The hydroxyl-protective group which can be used includes, for example, C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, C_{7-10} aralkyl group (e.g. benzyl, etc.), formyl, C_{1-6} alkyl-carbonyl group (e.g. acetyl, propionyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), tetrahydropyranyl, tetrahydrofuranyl, and silyl. These groups may respectively have 1 to 3 substituents, for example, halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl (methyl, ethyl, n-propyl, etc.), phenyl, C_{7-10} aralkyl (e.g. benzyl, etc.) and nitro.

Thes protective groups can be removed by th per

s known proc dures or any procedures analogous thereto. For example, a process using an acid, a base, a reducing agent, an ultraviolet light, hydrazine, phenylhydrazine, N-methyldithiocarbamate, tetrabutylammonium fluoride or palladium acetate can be utilized.

The salt of the compound (I) or (II) include, for example, salts with inorganic bases, salts with organic bases, salts with inorganic acids and salts with basic or acidic amino acids. The preferred salts with inorganic bases include, for example, alkaline metal salt (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.) and aluminum salt and ammonium salt. The preferred salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. The preferred salts with inorganioc acids include, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. The preferred salts with organic acids include, for example, salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. The preferred salts with basic amino acids include, for example, salts with arginine, lysine, ornithine, etc. The preferred salts with acidic amino acids include, for example, salts with aspartic acid, glutamic acid, etc.

Among them, pharmaceutically acceptable salts are particularly preferred. In case the compound has a basic functional group in its molecule, the pharmaceutically acceptable salts include, for example,

inorganic salt such as hydrochloride, sulfate, phosphate, hydrobr mide, etc., or organic salt such as acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate, tartrate, etc. In case of having an acidic functional group, the pharmaceutically acceptable salts include, for example, inorganic salt such as alkaline metal salt (e.g. sodium salt, potassium salt, etc.) or alkaline metal salt (e.g. calcium salt, magnesium salt, etc.) and ammonium salt.

The compounds (I) and (II) of this invention and their salts can be separated and purified by known procedures such as solvent extraction, pH change, redistribution, crystallization, recrystallization, chromatography, etc. The starting compounds of the compounds (I) and (II) of this invention and their salts can be separated and purified by the same known procedures as those described above, but the reaction mixture containing them may be respectively be submitted to the next reaction steps.

When the compounds (I) and (II) of this invention and their salts include optical isomers, stereoisomers, position isomers or rotational isomers, these are also included as the compounds of this invention and can be obtained by the per se known synthesis and isolation procedures. For example, when optical isomers exist in the compounds of this invention, optical isomers resolved from the compounds can also be included in this invention.

The optical isomers can be produced by the per se known method. Specifically, a desired optically active isomer can be obtained by using an optically active intermediate, or by optically resolving a mixture of racemic modifications as a final product according to a usual procedure.

As an optical r solution procedur , for example,

there can be used the following fractional recrystallization process, chiral column process, diastereomer process, etc,.

(1) Fractional recrystallization process

A process comprising reacting a racemic modification with an optically active compound to form a salt and separating the salt according to a fractional recrystallization method and optionally producing a free optical isomer through a neutralizing step.

(2) Chiral column process

A process of separating a racemic modification or a salt thereof using a column for separating an optical isomer (chiral column). In case of a liquid chromatography, for example, the optical isomer is separated by adding a mixture of optical isomers to a chiral column such as ENANTIO-OVM (manufactured by Toso Co.) and developing with water, various buffers (e.g. phosphate buffer, etc.) and an organic solvent (e.g. ethanol, methanol, acetonitrile, etc.) alone or in combination thereof. In case of a gas chromatography, it is separated by using a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Science Co.).

(3) Diastereomer process

A process comprising reacting a mixture of racemic modifications with an optically active reagent to form a mixture of diasteromers, separating the mixture into a single substance through normal means (e.g. fractional recrystallization, chromatography, etc.) and cleaving the optically active reagent site due to a chemical treatment such as hydrolysis reaction. For example, when the compound of this invention has a hydroxyl group or a primary or secondary amino group in the molecule, a diastereomer as an ester or amide can be obtained by subjecting the compound and an optically active organic acid (e.g.

MPTA[α-m thoxy-α-(trifluoromethyl)phenylacetic acid, (-)-menthoxyacetic acid, etc.) to a condensation reaction. On the other hand, when the compound of this invention has a carboxylic group, the diastereomer as the ester or amide can be obtained by subjecting the compound and an optically active amine or an alcohol reagent to a condensation reaction. The separated diastereomer is converted into an optical isomer of the original compound by subjecting to an acid hydrolysis or basic hydrolysis reaction.

The compounds (I) and (II) of this invention and their salts can be safely administered as they are or as a pharmaceutical composition containing a medicinally acceptable carrier in various dosage forms such as tablest (inclusive of dragees and film-coated tablets), powders, granules, capsules (inclusive of soft capsules), solutions, injections, suppositories, controlled-release preparations, etc. by the oral route or parenteral route (e.g. local, rectal or intravenous administration) according to the per se known method. An amount of the compound (I) or a salt thereof contained in the preparation of this invention is from 0.1 to 100% by weight based on the total weight. The dosage is dependent on the subject, route of administration, administration route, diseases, etc., but for the treatment of viral encephalitis, etc., for instance, the recommend oral regimen for an adult patient (b.wt. 60 kg) is about 0.1 to 500 mg/day, preferably about 1 to 100 mg/day, more preferably about 5 to 100 mg/day, to be administered once a day or in a few divided doses daily.

The pharmaceutically acceptable carrier includes a variety of organic and inorganic carriers or vehicles which are commonly used in the pharmaceutical field. Here, excipients, lubricants, binders, disintegrators, tc. are all subsumed in the concept of carrier for

solid preparations, while solvents, solubilizers, suspending agents, isotonizing agents, buff rs, anallgesics, etc. can be used in the formulation of liquid preparations. Where necessary, various additives such as preservatives, antioxidants, coloring agents, sweeteners, absorbents, moistening agents, etc. can also be added. The preferred excipient includes lactose, sucrose, D-mannitol, starch, corn starch, crystalline cellulose, and light silicic anhydride. The lubricant include magnesium stearate, calcium stearate, talc, and colloidal silica.

The binder includes crystalline cellulose, saccharose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, and carboxymethylcellulose.

The disintegrator includes starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethylstarch sodium, and L-hydroxypropylcellulose. The solvent include water for injection, alcohol, propylene glycol, macrogols, sesame oil, and corn oil.

The solubilizer includes polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, choresterol, triethanolamine, sodium carbonate, and sodium citrate.

The suspending agent includes surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, and glycerin monostearate, etc. and hydrophilic macromolecular substances such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose.

The isotonizing ag nt includ s glucose,

D-sorbitol, sodium chl ride, glyc rin, D-mannitol, etc.

The buffer includes various buff r solutions such as phosphate, acetate, carbonate, and citrate.

The anallgesic includes benzyl alcohol.

The preservative includes paraoxybenzoate, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, and sorbic acid.

The antioxidant includes sulfite, and ascorbic acid.

The drug comprising the diphenylmethane derivative of this invention and it's medicinally acceptable salt have an excellent MIP-1α/RANTES receptor antagonism and, therefore, they are useful as an medicament for mammals (e.g. humans, dogs, cats, rats, mice, bovines, etc.) for preventing or treating viral diseases or infectionary diseases (e.g. acute viral encephalitis, acute bacterial meningitis, Hericobacter pirolli infectious disease, pneumonia, hapatitis A, hepatitis B, hepatitis C, herpes simplex virus infectious disease, vesicle-strip blister virus infectious disease, HIV infectious disease (AIDS), influenza infectious disease, invasive staphylococcosis, tuberculosis, etc.), tumors (e.g. bladder cancer, mammary cancer, cervical carcinoma, chronic lymphatic leukemia, chronic myelocytic leukemia, colon cancer, multiple myeloma, malignant myeloma, prostatic cancer, lung cancer, stomach cancer, Hodgkin's disease, etc.), allergic diseases (e.g. bronchial asthma, atopic dermatitis, allergic rhinitis, etc.), inflammatory disease (e.g. arteriosclerosis, arterial sclerosis broken out after heart transplantation, (chronic) rheumatism, etc.), diabetic diseases (e.g. diabetes, diabetic nephropathy, diabetic complication, diabetic retinopathy, diabetic microangiopathy, etc.), central diseases (e.g. Alzheimer's disease, epilepsy, fever, ache, dementia, etc.), hyperlipemia,

hyperchlosterolemia, thrombocytopenia du to dialysis, spinal cord injury, osteoporosis, ulcerative colitis, peptic ulcer, sepsis (shock), reperfusion disorder of lung and heart, unstable angina pectoris, transient ischemic attack, valvular disease of heart, rejection after organ transplantation, retenosis after angioplasty, systematic lupus erythematosus, multiple sclerosis, renal failure, endometriosis, fibroid lung, adult respiratory distress syndrome, cardiac dysrhythmia, etc. Particularly, they are useful for preventing or treating allerigic diseases, inflammatory diseases or multiple sclerosis.

The compound used for MIP-1α/RANTES receptor antagonism of this investion is low toxic and has a low risk of side effect. The oral acute toxicity (LD_{50}) of the compound of this invention in rats is not less than 100 mg/kg.

[Mode of Working the Invention]

The following reference, working, formulation and test examples are intended to describe this invention in further detail, but they are mere examples and should by no means be construed as defining the scope of the invention. Thus, various modifications can be made without departing from the scope of the invention.

In the following reference and working examples, the term "room temperature" means any temperature within the range of 0 to 30°C. The organic solvents were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate. "%" means percent by weight otherwise specified. The other symbols have the following meanings.

s: singlet
d: doublet
t: triplet
q: quartet
m: multiplet

br:	broad
J:	coupling constant
Hz:	Herz
$CDCl_3$:	deuterochloroform
THF:	tetrahydrofuran
DMF:	N,N-dimethylformamide
DMSO:	dimethyl sulfoxide
^1H-NMR:	proton nuclear magnetic resonance (The sample was measured in a free form and when a conformational isomer existed, the only main peak was read.)
DMEM:	Dulbecco's modified Eagle's medium
PBS:	phosphate buffered saline

[Examples]

Reference Example 1-1:

3,3-Diphenyl-3-formylpropionitrile

To a solution of diphenylacetaldehyde (1 g) in tetrahydrofuran (10 ml) was added dropwise slowly a suspension of 60% sodium hydride (0.25 g) in tetrahydrofuran (5 ml) under ice-cooling and stirring. After completion of dropwise addition, the mixture was further stirred for 20 minutes. Then, bromoacetonitrile (0.41 ml) was added and the mixture was further stirred for 30 minutes. The reaction mixture was poured into ice-water and the oil that had separated out was extracted with ethyl acetate. The organic layer was taken, washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was purified by silica gel column chromatography to provide the titled compound (0.85 g) as colorless oil.

Reference Example 1-2:

4,4-Diphenyl-4-formylbutyronitrile

Diphenylacetaldehyde (25.6 g), acrylonitrile (12.5 ml) and DBU (2.5 g) were stirred in isopropyl alcohol (250 ml) with warming at 70°C for 6 hours. The reaction mixture was concentrated to dryness and the residue was purified by silica gel column chromatography. The crude crystal crop obtained was washed with isopropyl ether to provide the titled compound (19.8 g) as colorless prisms.

The structural formulas and NMR spectra of the respective compounds are shown in Table 1.

Reference Example 2-1:

Ethyl 5-cyano-4,4-diphenyl-2-pentenoate

3,3-Diphenyl-3-formylpropionitrile (0.85 g) and (carboethoxymethylene)triphenylphosphorane (1.46 g) were heated in chloroform (20 ml) under reflux for 7 hours. The reaction mixtur was then concentrated to

dryness and the residue was purified by silica gel column chromatography t provide the titled compound (0.7 g) as colorless oil.

The compound of Reference Example 2-2 was synthesized in the same manner as Reference Example 2-1.

Reference Example 2-2:

Ethyl 6-cyano-4,4-diphenyl-2-hexenoate

The structural formulas and NMR spectra of the above compounds are shown in Table 2.

Reference Example 3-1:

(4-Chlorophenyl)phenylacetonitrile

To a mixture of mandelonitrile (5 g) and chlorobenzene (15.7 g) was added sulfuric acid (9.8 ml) dropwise while the temperature of the mixture was maintained at 5°C - 10°C. After completion of dropwise addition, the mixture was stirred for another 1.5 hours. The reaction mixture was poured into ice-water and the syrup that had separated out was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was purified by silica gel column chromatography to provide the titled compound (3.6 g) as pale yellow syrup.

The compounds of Reference Examples 3-2 and 3-3 were synthesized in the same manner as Reference Example 3-1.

Reference Example 3-2:

(4-Methoxyphenyl)phenylacetonitrile

Reference Example 3-3:

Bis(4-chlorophenyl)acetonitrile

The structural formulas and NMR spectra of the respective compounds are shown in Table 3.

Reference Example 4-1:

Ethyl 4-cyano-4,4-diphenylbutyrat

To a solution of diphenylacetonitrile (28 g) in ethanol (100 ml) were added DBU (6 ml) and ethyl acrylate (30 ml). The mixture was heated and stirred at 80°C for 16 hours. After cooling, 2N-hydrochloric acid (200 ml) was added and the mixture was extracted with isopropyl ether. The organic extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude crystal crop was recrystallized from hexane-isopropyl ether to provide the titled compound (34 g).

The compounds of Reference Example 4-2 - 4 were synthesized in the same manner as Reference Example 4-1.

Reference Example 4-2:

Ethyl 4-(4-chlorophenyl)-4-cyano-4-phenylbutyrate

Reference Example 4-3:

Ethyl 4-cyano-4-(4-methoxyphenyl)-4-phenylbutyrate

Reference Example 4-4:

Ethyl 4,4-bis(4-chlorophenyl)-4-cyanobutyrate

Reference Example 4-5:

Ethyl 5-cyano-5,5-diphenylpentanoate

To a stirring solution of diphenylacetonitrile (1 g) in tetrahydrofuran (10 ml) was added 60% sodium hydride (0.25 g) in small portion under ice-cooling. After completion of dropwise addition, the mixture was stirred for 20 minutes. Then, ethyl 4-bromobutyrate (0.94 ml) was added dropwise under ice-cooling and the mixture was further stirred at room temperature for 15 minutes. The reaction mixture was poured into ice-water and the organic layer that had separated out was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was purified by silica gel column chromatography to provide the titled compound (0.87 g) as colorless oil.

Reference Example 4-6:

Ethyl 5-cyano-4,4-diphenylp ntanoat

To a solution of ethyl 5-cyano-4,4-diphenyl-2-pentenoate (0.7 g) in ethanol (20 ml) was added 10% palladium-on-carbon (0.24 g), and the mixture was reduced by catalytic hydrogenation at atmospheric pressure and at room temperature. The catalyst in the reaction mixture was filtered off and the filtrate was concentrated to dryness. The residue was purified by silica gel column chromatography to provide the titled compound (0.6 g) as colorless oil.

The compound of Reference Example 4-7 was synthesized in same manner as Reference Example 4-6.

Reference Example 4-7:

Ethyl 6-cyano-4,4-diphenylhexanoate

The structural formulas and NMR spectra of the respective compounds are shown in Table 4.

Reference Example 5-1:

5-Amino-4,4-diphenylpentanol

To a stirred solution of ethyl 4-cyano-4,4-diphenylbutyrate (1.2 g) in tetrahydrofuran (30 ml) was added lithium aluminum hydride (0.44 g) in small portion under ice-cooling. After completion of dropwise addition, the mixture was heated and stirred at 60°C for 3 hours. The reaction mixture was then cooled with ice again, water (1 ml) and 15% aqueous sodium hydroxide (3 ml) were added in succession. The insoluble matter that had separated out was filtered off and the filtrate was extracted with ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic layer was taken, washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was washed with isopropyl ether to provide the titled compound (0.82 g) as colorless powder.

The compounds of Reference Examples 5-2 - 7 were synthesized in the same manner as Reference Example 5-1.

Referenc Exampl 5-2:

5-Amino-4-(4-chlor phenyl)-4-phenylpentanol

Reference Example 5-3:

5-Amino-4-(4-methoxyphenyl)-4-phenylpentanol

Reference Example 5-4:

5-Amino-4,4-bis(4-chlorophenyl)pentanol

Reference Example 5-5:

6-Amino-5,5-diphenylhexanol

Reference Example 5-6:

6-Amino-4,4-diphenylhexanol

Reference Example 5-7:

7-Amino-4,4-diphenylheptanol

The structural formulas and NMR spectra of the respective compounds are shown in Table 5.

Reference Example 6-1:

5-Formylamino-4,4-diphenylpentanol

5-Amino-4,4-diphenylpentanol (10 g) was dissolved in formic acid (80 ml) followed by addition of acetic anhydride (13 ml). The mixture was stirred at room temperature for 4 hours and concentrated to dryness. The residue was partitioned between chloroform and water. The water layer was made basic with aqueous ammonia and extracted with chloroform. The extracts were dried over anhydrous sodium sulfate and concentrated to dryness. The residue was dissolved in ethanol (30 ml) and the solution was stirred in 1N-aqueous sodium hydroxide (20 ml) at room temperature for 20 minutes. The reaction mixture was diluted with water and the crystals that separated out were collected by filtration. The crystal was washed serially with water and ethyl acetate to provide the titled compound (9 g) as colorless powder.

The compounds of Reference Example 6-2 - 7 were synthesized in the same manner as Reference Example 6-1.

Reference Example 6-2:

4-(4-Chlorophenyl)-5-formylamino-4-phenylp ntanol

Reference Example 6-3:

5-Formylamino-4-(4-methoxyphenyl)-4-phenylpentanol

Reference Example 6-4:

4,4-Bis(4-chlorophenyl)-5-(formylamino)pentanol

Reference Example 6-5:

6-Formylamino-5,5-diphenylhexanol

Reference Example 6-6:

6-Formylamino-4,4-diphenylhexanol

Reference Example 6-7:

7-Acetylamino-4,4-diphenylheptanol

The structural formulas, physical properties, and NMR spectra of the above compounds are shown in Table 6.

Reference Example 7-1:

5-Formylamino-1-iodo-4,4-diphenylpentane

To a solution of 5-formylamino-4,4-diphenylpentanol (38.3 g) in methylene chloride (600 ml) were added p-toluenesulfonyl chloride (29.2 g), triethylamine (15 g), and 4-(dimethylamino)pyridine (catalytic amount). The mixture was stirred at room temperature for 4 hours and concentrated to dryness. The residue was stirred with Sodium Iodide (46.6 g) in acetone (600 ml) for 2 hours at 50°C. The reaction mixture was concentrated to dryness and the residue was diluted with ethyl acetate and water. The organic layer was taken, washed with an aqueous solution of sodium thiosulfate, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was purified by silica gel column chromatography to provide the titled compound (46.5 g) as yellow syrup.

The compounds of Reference Example 7-3 - 7 and 7-9 were respectively synthesized in the same manner as Reference Example 7-1.

R ference Exampl 7-2:

1-Iodo-4,4-diphenyl-5-(tosylamino)pentan

A mixture of 5-amino-4,4-diphenylpentanol (1 g), p-toluenesulfonyl chloride (1.65 g), triethylamine (1.2 ml), and 4-(dimethylamino)pyridine (catalytic amount) in methylene chloride (20 ml) were stirred at room temperature for overnight. The reaction mixture was concentrated to dryness and the residue was stirred with sodium iodide (0.7 g) in acetone (25 ml) at 50°C for 24 hours. The reaction mixture was concentrated to dryness and the residue was diluted with ethyl acetate and water. The separated organic layer, was dried over anhydrous sodium sulfate and concentrated to dryness to provide the titled compound (1 g) as light-yellow powder.

The compound of Reference Example 7-8 was synthesized in the same manner as Reference Example 7-2.

Reference Example 7-3:

4-(4-Chlorophenyl)-5-formylamino-1-iodo-4-phenyl-pentane

Reference Example 7-4:

5-Formylamino-1-iodo-4-(4-methoxyphenyl)-4-phenylpentane

Reference Example 7-5:

4,4-bis(4-chlorophenyl)-5-formylaminopentyl-1-tosylate

Reference Example 7-6:

6-Formylamino-1-iodo-5,5-diphenylhexane

Reference Example 7-7:

6-Formylamino-1-iodo-4,4-diphenylhexane

Reference Example 7-8:

1-Iodo-4,4-diphenyl-6-(tosylamino)hexane

The structural formulas, physical properties, and NMR spectra of the respective compounds are shown in Table 7.

Ref renc Exampl 7-9:

7-Acetylamino-1-iodo-4,4-diphenylheptane

Reference Example 8:

7-(2-Tetrahydropyranyloxy)-4,4-diphenylheptanonitrile

A solution of 6-cyano-4,4-diphenyl-1-hexanoic acid (12.5 g) in THF (85 ml) was added to a suspension of sodium borohydride (1.97 g) in THF (85 ml) at room temperature and stirred for 10 minutes. To the reaction mixture was added a solution of iodine (5.46 g) in THF (85 ml) under ice-cooling and the mixture was stirred for 1 hour. 3N-hydrochloric acid (20 ml) was added and the reaction mixture was concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate-water. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure to provide 6-cyano-4,4-diphenyl-1-hexanol (13 g). To a solution of the obtained alcohol (13 g) in dichloromethane (150 ml) were added p-toluenesulfonic acid monohydrate (catalytic amount) and 3,4-dihydro-2H-pyran (4.98 g) under ice-cooling and stirred for 15 hours. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate (4:1) to give the titled compound (10 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.40(2H,m), 1.41-1.90(6H,m), 1.91-2.08(2H,m), 2.08-2.20(2H,m), 2.40-2.57(2H,m), 3.26-3.39(1H,m), 3.40-3.52(1H,m), 3.60-3.73(1H,m), 3.74-3.88(1H,m), 4.49(1H,br s), 7.02-7.40(10H,m)

Reference Example 9:

1-Formylamino-7-(2-tetrahydropyranyloxy)-4,4-diphenylheptane

A solution of 7-(2-tetrahydropyranyloxy)-4,4-diphenylheptanenitrile (16.8 g) in THF (100 ml) was

added to a suspension of lithium aluminum hydride (4.3 g) in THF (150 ml) under ice-cooling and stirred at 60°C for 8 hours. To the reaction mixture was added an aqueous 1N-sodium hydroxide solution and the precipitate that separated out was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate-water and separated. The organic layer was washed serially with water and a saturated aqueous sodium chloride solution. After drying, the solvent was distilled off under reduced pressure to provide 7-(2-tetrahydropyranyloxy)-4,4-diphenylheptanamine (17 g).

A solution of the obtained amine (3.7 g) in pyridine (25 ml) was added to a solution of formic acid in chloroform (2M, 20 ml) followed by addition of 1.3-dicyclohexylcarbodiimide (4, 12 g) in chloroform (25 ml) with stirring under ice-cooling and the mixture was stirred for 4 hours. The reaction mixture was concentrated under reduced pressure and the precipitate that had separated out was filtered off. The filtrate was concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate-water and the organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate (1:2) to give the titled compound (1.4 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.37(2H,m), 1.40-1.90(8H,m), 2.05-2.20(4H,m), 3.05-3.40(3H,m), 3.40-3.53(1H,m), 3.56-3.75(1H,m), 3.75-3.90(1H,m), 4.49(1H,br s), 5.20-5.60(1H,br), 7.05-7.33(10H,m), 8.12(1H,d)

Reference Example 10:

1-Formylamino-7-iodo-4,4-diphenylheptane

To a solution of 1-f rmylamino-7-(2-

tetrahydropyranyloxy)-4,4-diphenylheptane (1.4 g) in methan l (20 ml) was added p-toluenesulfonic acid monohydrate (catalytic amount) at room temperature and the mixture was stirred for 3 hours. The reaction mixture was concentrated under reduced pressure to provide 1-formylamino-7-hydroxy-4,4-diphenylheptane (1.2 g) as an oil.

The obtained oily substance was dissolved in dichloromethane (20 ml). To the solution were added a mixture of triethylamine (1 ml), 4-dimethylaminopyridine (catalytic amount), and p-toluenesulfonylchloride (687 ml) and the mixture was stirred for 3 hours. The reaction mixture was concentrated under reduced pressure and the obtained residue was dissolved in ethyl acetate-1N hydrochloric acid. The organic layer was separated, washed serially with water and saturated aqueous sodium chloride, and dried. The solvent was distilled off under reduced pressure to give 7-formylamino-4,4-diphenylheptyl 7-p-toluenesulfonate (1.3 g) as an oil.

To a solution of the obtained tosylate (1.3 g) in acetone (20 ml) was added sodium iodide (66 mg) and the mixture was stirred at 50°C for 4 hours. The reaction mixture was concentrated under reduced pressure and the obtained residue was dissolved in ethyl acetate-water. The organic layer was separated, washed serially with water and saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate (1:1) to give the titled compound (1.4 g).
Melting point: 119°C - 121°C.

Reference Example 11-1:

1-Benzyl-4-[3,5-bis(trifluoromethyl)phenyl]-4-hydroxypiperidine

To a solution of 3,5-bis(trifluoromethyl)-

bromobenzene (1.17 g) in THF (10 ml) was added magnesium (97 mg) and stirred under a alg n stream at 60°C for 2 hours. To the thus prepared Grignard reagent was added 1-benzyl-4-piperidone (379 mg) in THF (2 ml) and the mixture was stirred for 30 minutes. Saturated aqueous ammonium chloride solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic extract was washed serially with water and saturated aqueous sodium chloride and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate-hexane (1:4). The solvent was distilled off to give the titled compound (620 mg).

Melting point: 89°C - 90°C

The compounds of Reference Examples 11-2 and 11-3 were synthesized in a manner similar to that described above.

Reference Example 11-2:

1-Benzyl-4-(4-trifluoromethylphenyl)-4-hydroxypiperidine

^{1}H-NMR ($CDCl_3$) δ: 1.64-1.85(3H,m), 2.16(2H,dt), 2.46(2H,dt), 2.71(2H,d), 3.59(2H,s), 7.20-7.39(5H,m), 7.62(4H,ABq)

Reference Example 11-3:

1-Benzyl-4-(3,5-dichlorophenyl)-4-hydroxypiperidine

Melting point: 75°C - 77°C

Reference Example 12-1:

4-[3,5-Bis(trifluoromethyl)phenyl]-4-hydroxypiperidine

To a solution of 1-benzyl-4-[3,5-bis(trifluoromethyl)phenyl]-4-hydroxypiperidine (1 g) in methanol (5 ml) was added 10% palladium-on-carbon (100 mg) and the mixture was stirred under a hydrogen atmospher at room temperature for 2 hours. The

catalyst was filtered off and the filtrate was concentrated under reduced pressur to give the titled compound (600 mg).

Melting point: 209°C - 210°C

Reference Example 12-2:

In a manner similar to Reference Example 12-1, 4-(4-trifluoromethylphenyl)-4-hydroxypiperidine was synthesized.

Melting point: 115°C - 116°C

Reference Example 13

4-(3,5-Dichlorophenyl)-4-hydroxypiperidine

To a mixture of 1-benzyl-4-(3,5-dichlorophenyl)-4-hydroxypiperidine (200 ml) and potassium carbonate (276 mg) in toluene (5 ml) was added chloroethyl carbonate (217 mg) and the mixture was stirred at 60°C for 2 days. Water was added to the reaction mixture and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate (4:1) to give [4-(3,5-dichlorophenyl)-1-ethoxycarbonylpiperidin-4-yl] ethyl carbonate (190 mg) as an oil.

To a solution of the carbonate (190 mg) in ethanol (5 ml) was added 4N-potassium hydroxide solution (5 ml) and the mixture was heated under reflux for 15 hours. The solvent was distilled off under reduced pressure. To the residue were added water and ethyl acetate and stirred well. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure to give the titled compound (135 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.60-1.75(4H,m), 1.97(2H,dt), 2.91-

3.16(4H,m), 7.26(1H,d), 7.40(2H,d)

Refer nce Example 14:

4-(4-Chlorophenyl)piperidine

To a solution of 4-(4-chlorophenyl)-4-hydroxypiperidine (478 mg) in acetic acid (5 ml) was added sulfuric acid (0.5 ml) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was made basic with 4N-sodium hydroxide and extracted with ethyl acetate. The organic layer was washed serially with water and a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure to give 4-(4-chlorophenyl-1,2,5,6-tetrahydropyridine (350 mg). To a solution of 4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine (250 mg) in methanol (5 ml) and 4N-hydrochloric acid (2 ml) was added 10% palladium-on-carbon (150 mg) and the mixture was stirred under a hydrogen atmosphere at room temperature for 2.5 hours. The catalyst was filtered off and the filtrate was made basic with a 4N-aqueous sodium hydroxide solution followed by extraction with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure to give the titled compound (180 mg) as an oily substance. ^{1}H-NMR ($CDCl_3$) δ: 1.60(2H,dq), 1.70-2.05(3H,m), 2.50-2.83(3H,m), 3.19(2H,dr d), 7.15(2H,d), 7.26(2H,d)

Reference Example 15:

4-(4-Chlorophenyl)-4-hydroxyhexamethyleneimine

1) 1-Benzyl-4-(4-chlorophenyl)-4-hydroxyhexamethyleneimine

In a similar manner to Reference Example 11-1, the titled compound was synthesized from 1-benzylhexamethylenimin-4-one and 4-chlorobromobenzene. ^{1}H-NMR ($CDCl_3$) δ: 1.49-2.20(6H,m), 2.32-2.59(2H,m), 2.60-2.73(1H,m), 2.82-3.13(2H,m), 3.66(2H,ABq), 7.21-

7.43(9H,m)

2) 4-(4-Chloroph nyl-4-hydroxyhexamethyl neimine

To a mixture of 1-benzyl-4-(4-chlorophenyl)-4-hydroxyhexamethyleneimine (472 mg) and potassium carbonate (414 mg) in toluene (3 ml) was added ethyl vinylcarbonate (426 mg) under ice-cooling and stirred at room temperature for 30 minutes. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate (6:1) to give [4-(4-chlorophenyl)-1-vinyloxycarbonyl-hexamethyleneimin-4-yl] vinyl carbonate (400 mg). To a solution of the product in ethanol (5 ml) was added 4N-aqueous potassium hydroxide solution (5 ml) and the mixture was stirred at 60°C for 4 hours. The solvent was distilled off under reduced pressure. To the residue were added water and ethyl acetate and stirred well. The organic layer was separated washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure to give the titled compound (150 mg).

^{1}H-NMR ($CDCl_3$)δ: 1.50-2.85(9H,m), 2.85-3.01(1H,m), 3.17-3.30(1H,m), 3.30-3.50(1H,m), 7.23-7.45(4H,m)

Reference Example 16:

Ethyl 4-cyano-4-phenyl-4-(2-pyridyl)butanoate

To a suspension of 60% sodium hydride (13.2 g) in DMF (400 ml) was added a solution of phenylacetonitrile (35.1 g) in DMF (20 ml) under ice-cooling and the mixture was stirred for 30 minutes. A solution of 2-bromopyridine (47.4 g) in DMF (20 ml) was added to the mixture under ice-cooling and stirred at room temperatur for 2 hours. Th r action mixture was

dilut d with wat r and xtracted with ethyl acetate. The organic extract was wash d serially with water and a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure to give 22 g of phenyl(2-pyridyl)acetonitrile
^{1}H-NMR ($CDCl_3$)δ: 5.32(1H,s), 7.20-7.50(7H,m), 7.70(1H,dt), 8.60(1H,dd)

To a solution of phenyl(2-pyridyl)acetonitrile (19.4 g) in ethanol (250 ml) were added ethyl acrylate (13 g) and 1,8-diazabicyclo[5,4,0]-7-undecene (1.5 ml) and the mixture was heated to reflux for 5 hours. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate (4:1 - 3:1) to give the titled compound as an oily substance.
^{1}H-NMR ($CDCl_3$) δ: 1.23(3H,t), 2.40-2.52(2H,m), 2.70-2.92(1H,m), 2.93-3.15(1H,m), 4.10(2H,q), 7.19-7.55(8H,m), 7.68(1H,dt), 8.63(1H,d)

Reference Example 17:

4-Cyano-4-phenyl-4-(2-pyridyl) butanoic acid

To a solution of ethyl 4-cyano-4-phenyl-4-(2-pyridyl)butanoate (2.9 mg) in ethanol (10 ml) was added 1N-aqueous sodium hydroxide solution (15 ml) and the mixture was stirred at 60°C for 30 minutes. The reaction mixture was concentrated under reduced pressure and neutralized with 1N-hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure to give the titled compound (2.7 g).
^{1}H-NMR ($CDCl_3$) δ: 2.45-2.60(2H,m), 2.78(1H,ddd), 3.06(1H,ddd), 7.20-7.55(7H,m), 7.68(1H,dt), 8.63(1H,d)

Reference Example 18:

N-[4-Cyano-4-phenyl-4-(2-pyridyl)butylyl]-4-(4-chloroph nyl)-4-hydroxypiperidine

To a solution of 4-cyano-4-phenyl-4-(2-pyridyl) butyric acid (1.33 g), 4-(4-chlorophenyl)-4-hydroxypiperdine (1.3 g), and diethyl phosphorocyanidate (982 mg) in DMF (20 ml) was added triethylamine (606 mg) at room temperature and the mixture was stirred for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (1.5 g) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.62-2.00(4H,m), 2.21(1H,s), 2.35-2.57(2H,m), 2.70-2.93(1H,m), 2.94-3.14(2H,m), 3.37-3.74(2H,m), 4.53(1H,br d), 7.19-7.53(12H,m), 7.68(1H,dt), 8.62(1H,d)

Reference Example 19:

5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2-phenyl-2-(2-pyridyl)pentylamine 2hydrochloride

To a suspension of lithium aluminum hydride (380 mg) and aluminum chloride (1.3 g) in ether (20 ml) was added N-[4-cyano-4-phenyl-4-(2-pyridyl)butylyl]-4-(4-chlorophenyl)-4-hydroxypiperidine (465 mg) under ice-cooling and the mixture was stirred for 20 minutes. To the reaction mixture was added 1N-aqueous sodium hydroxide solution and the resulting solution was extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified silica gel column chromatography eluting with ethyl acetate-hexane (1:1). The solvent was distilled off and the residue was treated with 4N-hydrochloric acid/ethyl acetate to giv the titl d

compound (250 mg) as a noncrystallin powder.
^{1}H-NMR ($CDCl_3$) δ: 1.05-1.42(2H,m), 1.45-1.90(5H,m), 1.90-2.13(2H,m), 2.14-2.40(6H,m), 2.66(2H,br d), 3.39(2H,ABq), 6.98-7.47(11H,m), 7.55(1H,dt), 8.57(1H,d)

Reference Example 20:

4-Cyano-4,4-diphenyl butanoic acid

To a solution of ethyl 4-cyano-4,4-diphenylbutanoate (16.1 g) in THF (6 ml) was added 1N-sodium hydroxide solution (60.5 ml) and the mixture was stirred at room temperature for 16 hours. The solution was made acidic with concentrated hydrochloric acid, extracted with ethyl acetate and dried. The solvent was distilled off to give an oily residue. The residue was crystallized from isopropyl ether to give the titled compound (12.0 g).
Melting point: 164°C - 165°C

Reference Example 21:

4-(4-Chlorophenyl)-1-(4-cyano-4,4-diphenylbutyryl)-4-hydroxypiperidine

To a solution of 4-cyano-4,4-diphenylbutanoic acid (8.0 g), 4-(4-chlorophenyl)-4-hydroxypiperidine (6.4 g), and diethylphosphoro cyanidate (4.6 ml) in DMF (75 ml) was added triethylamine (8.4 ml) at 0°C and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into pure water (500 ml) and the solid that separated out was collected by filtration. The solid was dissolved in ethyl acetate, washed with a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The solid residue was suspended with ether and collected by filtration to give the titled compound (12.6 g). Melting point: 205°C - 206°C

Reference Example 22:

1-(5-Amino-4,4-diphenylpentanoyl)-4-(4-chloroph nyl)-4-hydroxypiperidin

To the suspension of 4-(4-chlorophenyl)-1-(4-cyano-4,4-diph nylbutyryl)-4-hydroxypiperidin (6.9 g) in saturated ammonia ethanol solution (500 ml) was added Reney-Cobalt catalyst (7 g) and the mixture was reacted under 5 atmospheric pressure of hydrogen for 8 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give an oily residue (5.4 g).

^{1}H-NMR ($CDCl_3$) δ: 1.57-1.89(4H,m), 1.99-2.08(2H,m), 2.43-2.53(2H,m), 3.01(1H,dt), 3.25(2H,s), 3.22-3.35(2H,m), 4.51(1H,br d), 7.15-7.37(14H,m)

Reference Example 23:

4-Cyano-4,4-diphenyl-1-butanol

To a solution of ethyl 4-cyano-4,4-diphenylbutanoate (44.0 g) in THF (440 ml) was added carefully lithium tetrahydroborate (3.9 g) at 0°C. Th reaction mixture was allowed to warm to room temperature and stirred for 2 days. The reaction mixture was poured into a cold 1N-hydrochloric acid (440 ml) and extracted with ethyl acetate. The organic extract was washed with saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:2) to give the titled compound (34.6 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.62-1.76(2H,m), 2.47-2.55(2H,m), 3.69(2H,t), 7.28-7.42(10H,m)

Reference Example 24:

1-Bromo-4-cyano-4,4-diphenylbutane

To a suspension of triphenylphosphine (27.5 g) in acetonitrile (100 ml) was added bromine (5.2 ml) dropwise at 0°C. After completion of dropwise addition, a solution of 4-cyano-4,4-diphenyl-1-butanol (25.1 g) in acetonitrile (40 ml) was added to the reaction mixture at 0°C and the mixture was stirred at

room temperature for 1 hour. The solvent was distill d off und r reduced pressur and ether was added to the obtained residue. Triphenylphosphineoxide was filtered off and the filtrate was washed with a saturated aqueous sodium chloride solution, dried, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with ether and crystallized from IPE to give the titled compound (25.6 g)

^{1}H-NMR ($CDCl_3$) δ: 1.93-2.07(2H,m), 2.527-2.61(2H,m), 3.44(2H,t), 7.26-7.42(10H,m).

Reference Example 25:

4-(4-Chlorophenyl)-1-(4-cyano-4,4-diphenylbutyl)-4-hydroxypiperidine

To a solution of 1-bromo-4-cyano-4,4-diphenylbutane (22.0 g) in acetonitrile (500 ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (17.8 g), potassium carbonate (29.0 g), and potassium iodide (1.2 g) and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off under reduced pressure. The residue was dissolved in ethyl acetate and washed with pure water. The organic layer was washed with a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (31.4 g) as a noncrystalline power.

^{1}H-NMR ($CDCl_3$) δ: 1.60-1.83(5H,m), 2.06(2H,dt), 2.30-2.49(6H,m), 2.71(2H,br d), 7.27-7.45(14H,m).

Reference Example 26:

1-Amino-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane

To a solution of 4-(4-chlorophenyl)-1-(4-cyano-4,4-diphenylbutyl)-4-hydroxypiperidine (31.3 g) in saturated ammonium-ethan l solution (500 ml) was added

Ran y-Co catalyst (20 g) and the mixture was stirred under 5 atmosph ric pressure of hydrogen gas for 8 hours at 70°C. The solvent was distilled off under reduced pressure. The obtained residue was crystallized from ethyl acetate to give the titled compound (17.8 g).

Melting point: 116°C - 117°C

Reference Example 27:

2-Benzoylthiophenecyanohydrin

A mixture of 2-benzoylthiophene (10 g), trimethylcyanide (6 g), and zinc iodide (0.15 g) acetonitrile (50 ml) was stirred at 50°C for 16 hours. The solvent was distilled off under reduced pressure. 1N-Hydrochloric acid (60 ml) and ethanol (30 ml) were added to the residue and the mixture was stirred at 55°C for 2 hours. The reaction mixture was extracted with isopropyl ether and the organic extract was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium choloride solution, respectively and dried. The solvent was distilled off under reduced pressure to give the titled compound (11.5 g).

^{1}H-NMR ($CDCl_3$) δ: 3.68(1H,br s), 6.98(1H,dd), 7.19(1H,dd), 7.34-7.46(4H,m), 7.59(2H,m).

Reference Example 28:

Phenyl-2-thienylacetonitrile

A solution of 2-benzoylthiophenecyanhydrin (250 mg) in ether (1 ml) and sodium borohydride (430 mg) were added to a solution of trifluoroacetic acid (5 ml) at 0°C and the mixture was stirred 15 hours at room temperature. The solvent was distilled off under reduced pressure. The residue was dissolved in 1N-aqueous sodium hydroxide and the water layer was extracted with ethyl acetate. The organic extract was washed with saturated aqueous sodium chloride and dried. The solv nt was distilled off und r reduc d

pressure and the obtained r sidue was purified by silica gel column chromatography eluting with hexane-ethyl ac tate (8:1) to give the titled compound (110 mg).

^{1}H-NMR ($CDCl_3$) δ: 5.35(1H,s), 6.97(1H,dd), 7.05-7.09(1H,m), 7.27(1H,dd), 7.32-7.44(5H,m).

Reference Example 29:

Ethyl 4-cyano-4-phenyl-4-(2-thienyl)butyrate

In a similar manner to Reference Example 4-1, the titiled compound was synthesized from phenyl-2-thienylacetonitrile.

^{1}H-NMR ($CDCl_3$) δ: 1.23(3H,t), 2.41(1H,dd), 2.56(1H,dd), 2.80(2H,dt), 4.10(2H,q), 6.96(1H,dd), 7.00(1H,dd), 7.25-7.52(6H,m).

Reference Example 30:

5-Formylamino-4-phenyl-4-(2-thienyl)pentanol

In a similar manner to Reference Example 4-1, ethyl 4-cyano-4-phenyl-4-(2-thienyl)butyrate was reduced to obtain 5-amino-4-phenyl-4-(2-thienyl)pentanol. Then in a similar manner to Reference Example 6-1, the titiled compound was obtained from 5-amino-4-phenyl-4-(2-thienyl)pentanol.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.59(2H,m), 1.81(1H,br s), 2.21(2H,t), 3.56(2H,t), 3.98(2H,dd), 4.12(2H,dd), 5.43(2H,br s), 6.85-7.00(2H,m), 7.10-7.40(6H,m), 8.11(1H,s).

Reference Example 31:

5-Formylamino-1-iodo-4-phenyl-4-(2-thienyl)pentane

By using iodination according to Reference Example 7-1, the titiled compound was obtained from 5-formylamino-4-phenyl-4-(2-thienyl)pentanol.

^{1}H-NMR ($CDCl_3$) δ: 1.48-1.75(2H,m), 2.08-2.28(2H,m), 3.10(2H,t), 4.03(2H,dd), 5.18-5.65(1H,br m), 6.84-7.00(2H,m), 7.15-7.40(6H,m), 8.12(1H,d).

Ref renc Example 32:

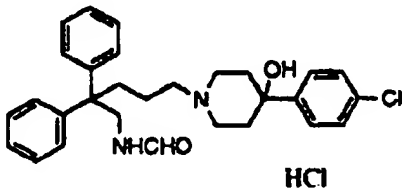
4-Chloromandelonitorile

To a aqueous sodium hydrogensulfite (53.2 g) (400 ml) was added 4-chlorobenzaldehyde (60 g) and the mixture was stirred at 40°C for 1 hour, cooled by 0°C, and ether (250 ml) was added. Sodium cyanide (22.6 g) in water (100 ml) was added to the mixture, and the mixture was stirred at 0°C for 2 hours. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried. The solvent was distilled off under reduced pressure to give the titled compound (65g).

^{1}H-NMR ($CDCl_3$) δ: 3.06(1H,br d), 5.53(1H,d), 7.38-7.52(4H,m).

Example 1-1

5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1-formylamino-2,2-diphenylpentane hydrochloride



HCl

To a solution of 5-formylamino-1-iodo-4,4-diphenylpentane (5 g) and 4-(4-chlorophenyl)-4-hydroxypiperidine (3.9 g) in acetonitrile (150 ml) was added potassium carbonate (7.7 g) and the mixture was stirred at 60°C for 15 hours. The solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the obtained residue and stirred well. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate. The solvent was distilled off and the residu was treated with 4N-hydrochloric acid/ethyl

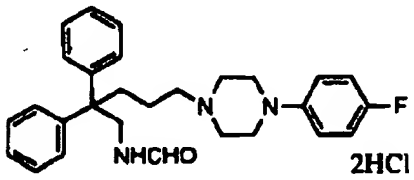
acetate to give the titled compound (5.6 g) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.40(2H,m), 1.58-1.92(3H,m), 1.93-2.22(4H,m), 2.23-2.42(4H,m), 2.65(2H,br d), 4.05(2H,d), 5.13(1H,br t), 7.10-7.28(14H,m), 8.09(1H,d).

The compounds of 1-2 to 1-10 were synthesized in a manner similar to Example 1-1.

Example 1-2

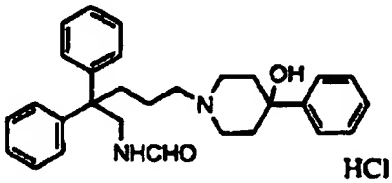
5-[4-(4-Fluorophenyl)piperadin-1-yl]-1-formylamino-2,2-diphenylpentane dihydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.20-1.40(2H,m), 2.10-2.40(4H,m), 2.45(4H,t), 3.05(4H,t), 4.06(2H,d), 5.10(1H,br s), 6.80-7.00(4H,m), 7.10-7.40(10H,m), 8.10(1H,d).

Example 1-3

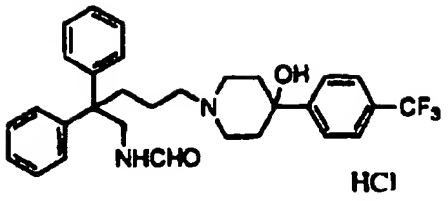
1-Formylamino-5-(4-hydroxy-4-phenylpiperidino)-2,2-diphenylpentane hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.22-1.45(2H,m), 1.72(2H,br d), 1.80-2.28(7H,m), 2.30-2.50(4H,m), 2.65-2.80(2H,m), 4.05(2H,d), 5.15-5.26(1H,br), 7.13-7.55(15H,m), 8.10(1H,d).

Example 1-4

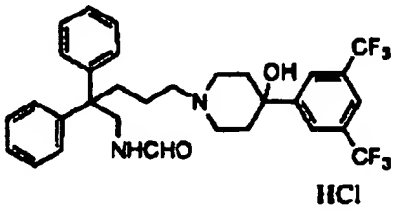
5-[4-(4-Trifluoromethylphenyl)-4-hydroxypiperidino]-1-formylamino-2,2-diphenylpentane hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.26-1.42(2H,m), 1.67(2H,br d), 1.81-2.26(4H,m), 2.27-2.45(4H,m), 2.73(2H,br d), 4.05(2H,d), 5.09-5.20(1H,br t), 7.13-7.37(10H,m), 7.55-7.70, 8.09(1H,d).

Example 1-5

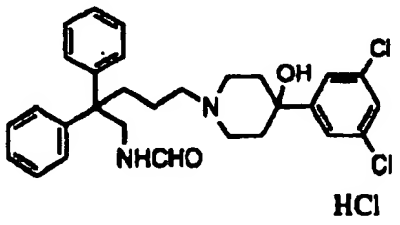
5-[4-[3,5-Bis (trifluoromethyl)phenyl]-4-hydroxy piperidino]-1-formylamino-2,2-diphenylpentate hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.15-1.40(2H,m), 1.67(2H,br d), 1.90-2.24(4H,m), 2.25-2.45(4H,m), 2.69(3H,br d), 4.03(2H,d), 5.22(1H,br t), 7.05-7.40(10H,m), 7.75(1H,s), 7.97(2H,s), 8.04(1H,d).

Example 1-6

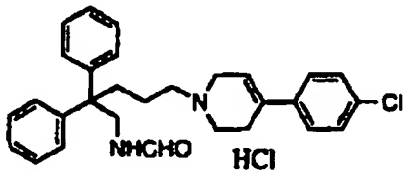
5-[4-(3,5-Dichlorophenyl)-4-hydroxypiperidino]-1-formylamino-2,2-diphenylpentane hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.15-1.40(2H,m), 1.64(2H,br d), 1.94-2.42(9H,m), 2.62-2.76(2H,m), 4.05(2H,d), 5.16(1H,br t), 7.10-7.43(13H,m), 8.08(1H,d).

Example 1-7

5-[4-(4-Choloph nyl)-1,2,3,6-tetrahydropyridin-1-yl]-1-formylamino-2,2-diphenylpentane hydrochloride



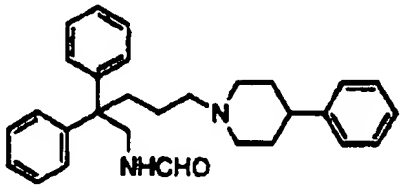
Recrystallization solvent: ethyl acetate/isopropyl ether

Melting point: 123°C - 125°C

Recrystallization solvent: ethyl acetate/isopropyl ether

Example 1-8

1-Formylamino-2,2-diphenyl-5-(4-phenylpiperidino)pentane

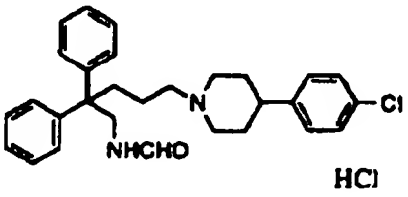


Recrystallization solvent: ethyl ether/hexane

Melting point: 133°C - 135°C

Example 1-9

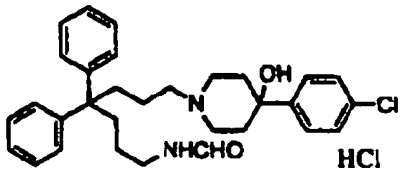
5-[4-(4-Chlorophenyl)piperidino]-1-formylamino-2,2-diphenylpentane hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.15-1.40(2H,m), 1.50-2.50(11H,m), 2.87(2H,br d), 4.05(2H,d), 5.00-5.25(1H,br), 7.00-7.40(14H,m), 8.09(1H,d).

Exampl 1-10

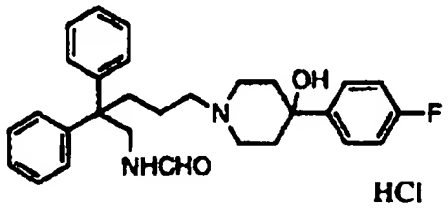
7-[4-(4-Chlorphenyl)-4-hydroxypiperidino]-1-formylamino 4,4-diphenylh ptane hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.12-1.30(4H,m),1.66(2H,br d), 1.77-2.22(7H,m), 2.22-2.43(4H,m), 2.56-2.72(2H,m), 3.22(2H,q), 5.40-5.64(1H,br), 7.10-7.35(12H,m), 7.42(2H,d), 8.08(1H,d).

Example 2-1

5-[4-(4-Fluorophenyl)-4-hydroxypiperidino]-1-formylamino-2,2-diphenylpentate hydrochloride



To a solution of 1-formylamino-5-iodo-2,2-diphenylpentane (1 g), 4-piperidone hydrochloride mono hydrate (450 mg) in acetonitrile (10 ml) was added potassium carbonate (845 g) and the mixture was stirred at 45°C for 2 days. The solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, and the mixture was stirred well. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate-methanol (9:1) to give 1-formylamino-2,2-diphenyl-5-(4-piperidon-1-yl)pentane (570 mg) as a noncrystalline powder.

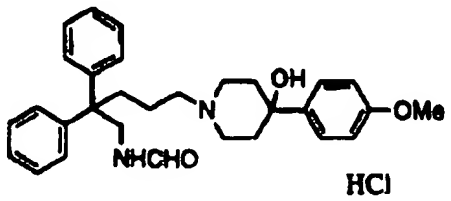
To a solution of 4-bromofluorobenzene (298 mg) in THF (5 ml) was added dropwise 1.6 M of n-butyl lithium hexane solution (1.25 ml) under an argon atmosphere at -78°C and the mixture was stirred for 20 minutes. Anhydrous cerium chloride (520 mg) was added to the reaction mixture, and the mixture was stirred for another 45 minutes followed by addition of a solution of 1-formylamino-2,2-diphenyl-5-(4-piperidon-1-yl)pentane (125 mg) in THF (1 ml). The reaction temperature was raised to -10°C gradually. After 1.5 hours, water and 1N-sodium hydroxide solution were added to the reaction mixture and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate-methanol (9:1). The solvent was distilled off and the obtained residue was treated with 4N-hydrochloric acid/ethyl acetate to give the titled compound (85 mg) as noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.42(2H,m), 1.50-1.95(3H,m), 2.00-2.23(4H,m), 2.24-2.44(4H,m), 2.70(2H,br d), 4.06(2H,d), 5.10-5.23(1H,br), 7.01(2H,t), 7.10-7.38(10H,m), 7.39-7.52(2H,m), 8.09(1H,d).

The compounds of Examples 2-2 and 2-3 were synthesized in a manner similar to Example 2-1.

Example 2-2

1-Formylamino-5-[4-hydroxy-4-(4-methoxyphenyl) piperidino]-2,2-diphenylpentane hydrochloride

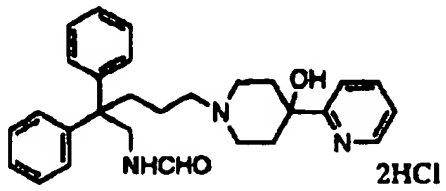


HCl

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.45(2H,m), 1.50-2.20(7H,m), 2.21-2.40(4H,m), 2.53-2.71(2H,m), 3.80(3H,s), 4.05(2H,d), 5.12-5.22(1H,br), 6.87(2H,d), 7.10-7.45(12H,m), 8.09(1H,d).

Example 2-3

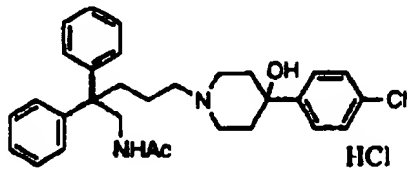
1-Formylamino-5-[4-hydroxy-4-(2-pyridyl)piperidino]-2,2-diphenylpentane dihydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.20-1.53(2H,m), 1.63(2H,br d), 2.16-3.06(11H,m), 4.06(2H,d), 5.32-5.42(1H,br), 7.03-7.40(11H,m), 7.48(1H,t), 7.73(1H,dt), 8.11(1H,d), 8.50(1H,d).

Example 3-1

1-Acetylamino-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride



To a mixture of 1-amino-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane (112 mg) (in ethyl acetate (3 ml)) was added a saturated aqueous sodium carbonate solution followed by addition of anhydrous acetic acid (24 mg) under vigorously stirring at 0°C and the mixture was stirred for 5 minutes. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica g l column chromatography eluting with ethyl acetat -

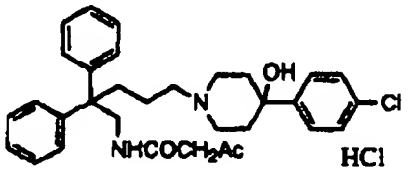
methanol (19:1). Th solvent was distilled off and th residue was tr ated with 4N-hydrochloric acid/ thyl acetate to give the titled compound (45 mg) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.42(2H,m), 1.68(2H,br d), 1.85(3H,s), 2.00-2.20(3H,m), 2.26-2.28(4H,m), 2.72(2H,br d), 3.98(2H,d), 5.02(1H,br t), 7.13-7.38(12H,m), 7.42(2H,d).

The compounds of Examples 3-2 to 3-12 were synthesized in a manner similar to Example 3-1.

Example 3-2

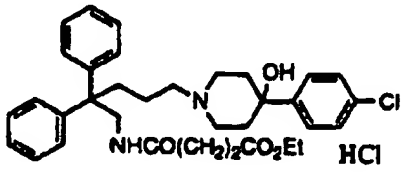
1-Acetoacetylamino-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.20-1.40(2H,m), 1.64(2H,br d), 1.80-2.20(8H,m), 2.20-2.40(4H,m), 2.65(2H,br d), 3.26(2H,s), 4.02(2H,d), 6.40-6.53(1H,br), 7.14-7.44(14H,m).

Example 3-3

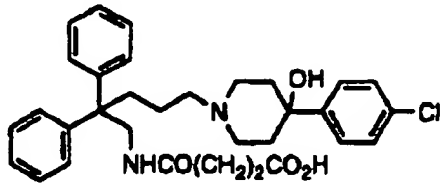
Ethyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]succinamate hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.17-1.38(5H,m), 1.65(2H,br d), 1.92-2.14(5H,m), 2.20-2.37(6H,m), 2.55-2.72(4H,m), 4.01(2H,d), 4.10(2H,q), 5.18(1H,br t), 7.16-7.38(12H,m), 7.43(2H,d).

Example 3-4

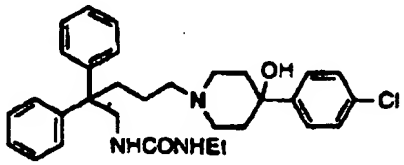
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-dipenylpentyl]succinamic acid



^{1}H-NMR (DMSO-d_6) δ: 1.08-1.29(2H,m), 1.53(2H,br d), 1.80-2.28(9H,m), 2.29-2.48(4H,m), 2.53-2.68(2H,m), 3.89(2H,br d), 7.10-7.39(12H,m), 7.48(2H,d).

Example 3-5

1-[5-[4-(4-Chlorphenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-ethylurea

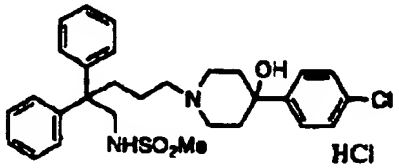


Recrystallization solvent: ethyl acetate/hexane

Melting point: 142°C - 144°C

Example 3-6

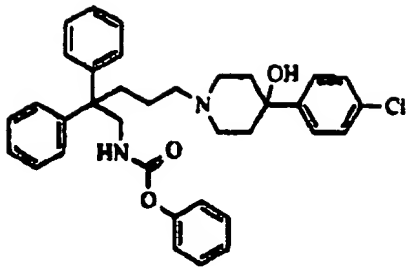
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]methanesulfonamide hydrochloride



^{1}H-NMR ($DCCl_3$) δ:1.20-1.36(2H,m), 1.60-1.80(3H,m), 2.00-2.43(8H,m), 2.48(3H,s), 2.71(2H,br d), 3,82(2H,d), 4.78-4.92(1H,br), 7.13-7.40(12H,m), 7.45(2H,d).

Example 3-7

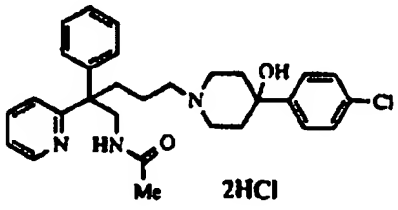
Phenyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2, 2-diphenylpentyl]carbamate



^{1}H-NMR ($CDCl_3$) δ: 1.22-1.42(2H,m), 1.53-1.74(2H,m), 1.96-2.40(9H,m), 2.19(2H,br d), 4.02(2H,d), 4.89(1H,br t), 6.95-7.08(2H,m), 7.10-7.46(17H,m).

Example 3-8

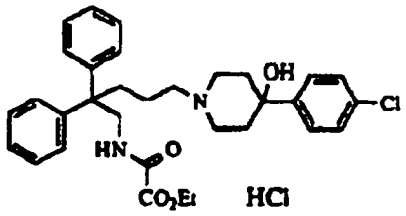
1-Acetylamino-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2-phenyl-2-(2-pyridyl)pentane dihydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.15-1.50(2H,m), 1.67(2H,br d), 1.85(3H,s), 1.94-2.48(8H,m), 2.50-2.76(3H,m), 3.87(1H,dd), 4.13(1H,dd), 6.58(1H,br t), 6.95-7.52(11H,m), 7.60(1H,dt), 8.57(1H,dt).

Example 3-9

Ethyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]oxamate hydrochloride

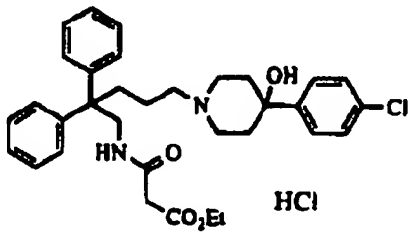


^{1}H-NMR ($CDCl_3$) δ: 1.15-1.40(5H,m), 1.64(2H,br d), 1.71-2.18(5H,m), 2.19-2.38(4H,m), 2.56-2.69(2H,m),

4.05(2H,d), 4.26(2H,q), 6.72(1H,br t), 7.14-7.44(14H,m).

Example 3-10

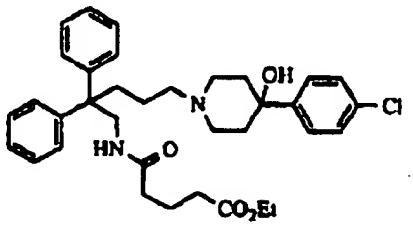
Ethyl N-[5-[4-(4-chlorophenyl)-4-hdyroxypiperidino]-2,2-diphenylpentyl]malonamate hydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.15-1.38(5H,m), 1.64(2H,d), 1.95-2.19(5H,m), 2.20-2.38(4H,m), 2.57-2.70(2H,m), 3.17(2H,s), 3.98-4.15(4H,m), 6.58(1H,br t), 7.16-7.45(14H,m).

Example 3-11

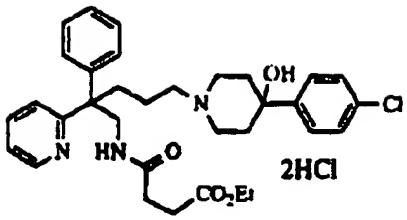
Ethyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]glutaramate



^{1}H-NMR ($CDCl_3$) δ: 1.13-1.40(5H,m), 1.58-1.94(5H,m), 1.95-2.16(6H,m), 2.17-2.39(6H,m), 2.66(2H,br d), 4.01(2H,d), 4.09(2H,q), 5.05(1H,br t), 7.15-7.38(12H,m), 7.43(2H,d).

Example 3-12

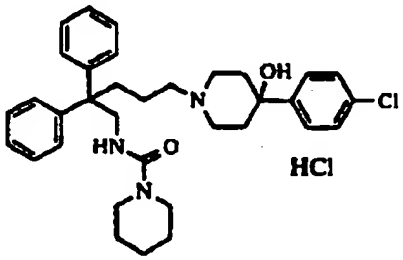
Ethyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2-phenyl-2-(2-pyridyl)pentyl]succinamate dihydrochloride



^{1}H-NMR ($CDCl_3$) δ: 1.18-1.50(5H,m), 1.88-2.10(3H,m), 2.10-2.48(8H,m), 2.49-2.74(6H,m), 3.89(1H,dd), 4.05-4.20(3H,m), 6.66(1H,br t), 7.05-7.37(11H,m), 7.60(1H,dt), 8.56-8.62(1H,m).

Example 4-1

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-pentamethyleneurea hydrochloride



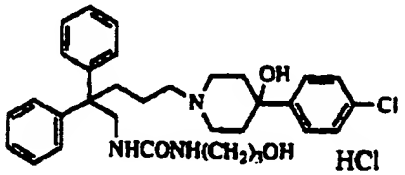
To a solution of phenyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl] carbamate (86 mg) and piperidine (43 mg) in DMF (1 ml) was added potassium carbonate (69 mg) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purrified by silica gel column chromatography eluting with ethyl acetate-methanol (20:1). The solvent was distilled off and the obtained residue was treated with 4N-hydrochloric acid/ethyl acetate to give the titled compound (80 mg) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.60(2H,m), 1.66(2H,br d), 1.80-

2.20(5H,m), 2.20-2.40(4H,m), 2.67(2H,br d), 3.06-3.13(4H,m), 3.95(2H,s), 7.17-7.38(12H,m), 7.43(2H,d).

Example 4-2

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-hydroxypropyl)urea hydrochloride

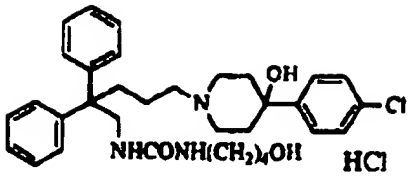


To a solution of phenyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl] carbamate (569 mg) and 3-amino-1-propanol (113 mg) in DMF (2 ml) was added potassium carbonate (267 mg) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate-methanol (9:1). The solvent was distilled off and the residue was treated with 4N-hydrochloric acid/ethyl acetate to give the titled compound (600 mg) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.40(2H,m), 1.40-1.72(4H,m), 1.75-2.18(6H,m), 2.23-2.43(4H,m), 2.70(2H,br d), 3.24(2H,q), 3.56(2H,t), 3.92(2H,d), 4.18(1H,br t), 4.48(1H,br t), 7.18-7.48(14H,m).

Example 4-3

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(4-hydroxybutyl)urea hydrochloride



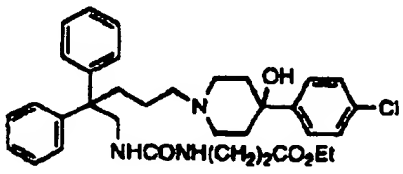
To a solution of phenyl N-[5-[4-(4-chlorphenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]carbamate (235 mg) and 4-amino-1-butanol (67 mg) in DMF (1 ml) was added potassium carbonate (138 mg) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate-methanol (9:1). The solvent was distilled off and the residue was treated with 4N-hydrochloric acid/ethyl acetate to give the titled compound (205 mg) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.43(2H,m), 1.45-1.56(2H,m), 1.68(2H,d), 1.90-2.52(12H,m), 2.76(2H,br d), 3.07(2H,q), 3.61(2H,t), 3.94(2H,d), 4.08(1H,br t), 4.53(1H,br t), 7.14-7.48(14H,m).

The compounds of Examples 4-4 to 4-10 were synthesized in the same manner as Example 4-1.

Example 4-4

Ethyl 3-[3-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]ureido]propionate

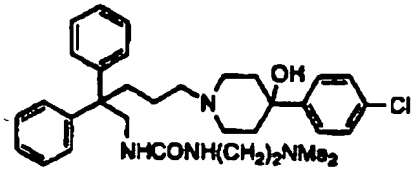


Recrystallization solvent: ethyl acetate/hexane

Melting point: 108°C - 110°C

Example 4-5

1-[5-[4-(4-Chlorphenyl)-4-hydr xypiperidino]-2,2-diphenylpentyl]-3-(2-dimethylaminoethyl)urea

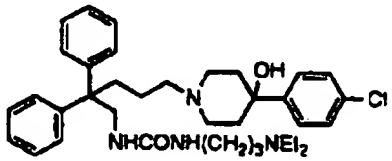


Recrystallization solvent: ethyl acetate/ether

Melting point: 104°C - 105°C

Example 4-6

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-diethylaminopropyl)urea

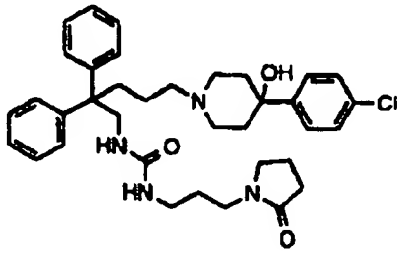


Recrystallization solvent: ethyl acetate/ether

Melting point: 122°C - 124°C

Example 4-7

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[3-(2-pyrrolidon-1-yl)propyl]urea

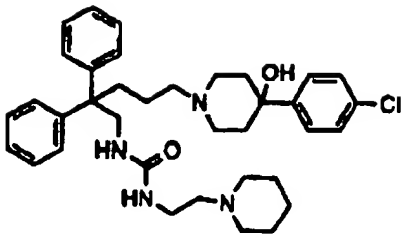


Recrystallization solvent: ether

Melting point: 115°C - 116°C

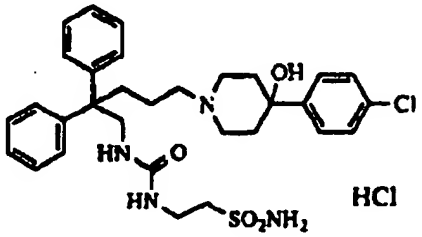
Example 4-8

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(2-piperidinoethyl)urea



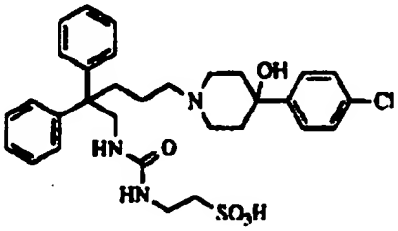
Recrystallization solvent: eher/hexane
Melting point: 122°C - 123°C
Example 4-9

2-[3-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]ureido]ethanesulfonamide hydrochloride



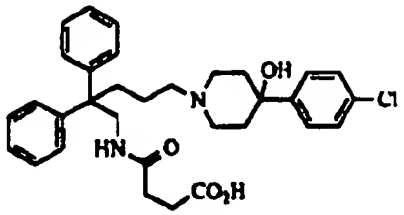
Recrystallization solvent: ehtyl ether/isopropyl ether
Melting point: 142°C - 145°C
Example 4-10

2-[3-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]ureido]ethanesulfonic acid



Recrystallization solvent: methanol/isopropyl ether
Melting point: 221°C - 224°C
Example 5-1

N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]succinamic acid



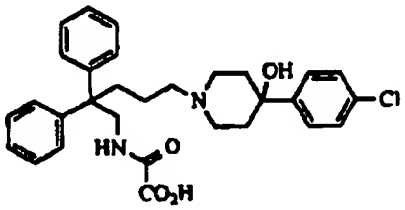
To a solution of ethyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl] succinamate (1.05 g) in ethanol (10 ml) was added 1N-aqueous sodium hydroxide solution (3 ml) and the mixture was stirred at 60°C for 2 hours. The reaction mixture was concentrated, diluted with water, neutralized with 1N-hydrochloric acid and extracted with ethyl acetate. The organic extract was dried and the solvent was distilled off under reduced pressure to give the titled compound (900 mg).

Melting point: 180°C - 182°C

The compounds of Examples 5-2 to 5-5 were synthesized in the same manner as Example 5-1.

Example 5-2

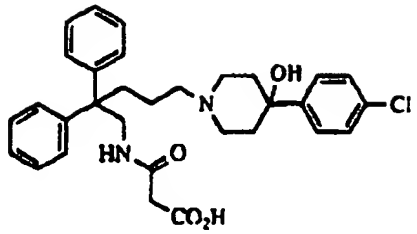
N-[5-[4-(4-chlorophenyl)-4-hdyroxypiperidino]-2,2-diphenylpentyl]oxamic acid



^{1}H-NMR (DMSO-d_6) δ: 1.08-1.40(2H,m), 1.40-1.65(2H,m), 1.75-2.90(9H,m), 3.10-3.50(2H,m), 3.90(2H,br d), 4.80-5.40(1H,br), 7.12-7.50(14H,m).

Example 5-3

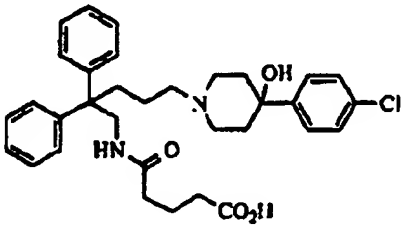
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]malonamic acid



^{1}H-NMR (DMSO-d_6) δ: 1.17-1.30(2H,m), 1.46-1.63(2H,m), 1.80-2.10(3H,m), 2.10-2.60(6H,m), 2.70-3.20(4H,m), 3.80-3.92(2H,m), 6.64-6.90(1H,br), 7.00-7.33(14H,m).

Example 5-4

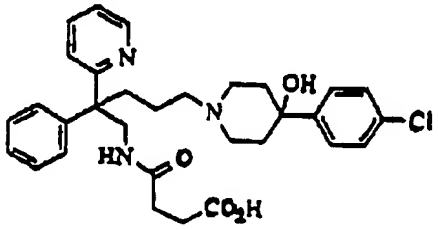
N-[5-[4-(4-chlrophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]glutamic acid



^{1}H-NMR (DMSO-d_6) δ: 1.05-1.30(2H,m), 1.40-1.66(4H,m), 1.70-2.15(9H,m), 2.20-2.26(4H,m), 2.52-2.66(2H,m), 3.90(2H,d), 4.30-5.70(2H,br), 7.07-7.39(12H,m), 7.46(2H,d).

Example 5-5

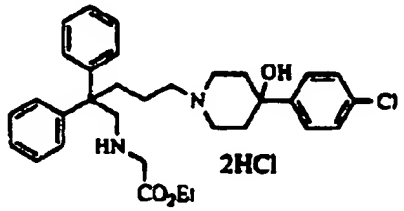
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2-phenyl-2-(2-pyridyl)pentyl]succinamic acid



^{1}H-NMR (DMSO-d_6) δ: 1.05-1.52(2H,m), 1.55-1.72(2H,m), 1.90-2.50(9H,m), 2.60-3.13(6H,m), 3.83-4.20(2H,m), 5.00-5.60(1H,br), 7.03-7.50(11H,m), 7.62-7.73(1H,m), 8.53(1H,d).

Example 6-1

N-[5-[4-(4-Chlorophenyl)-4-hydroxypip ridino]-2,2-diphenylpentyl]glycine ethyl ester dihydrochloride



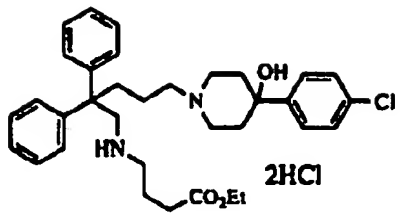
To a solution of 1-amino-5-[4-(4-chlorophenyl)-4-hdyroxypireridino]-2,2-diphenyl)pentane (340 mg) and potassium carbonate (414 mg) in acetonitrile (5 ml) was added ethyl bromoacetate (134 mg) and the mixture was stirred at 60°C for 2.5 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed serially with water and a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography eluting with ethyl acetate-methanol (20:1). The solvent was distilled off and residue was treated with 4N-hydrochloric acid/ethyl acetate to give the titled compound (200 mg) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.36(5H,m), 1.50-1.85(4H,m), 2.06(2H,dt), 2.16-2.42(6H,m), 2.67(2H,br d), 3.26(2H,s), 3.31(2H,s), 4.12(2H,q), 7.14-7.35(12H,m), 7.43(2H,d).

The compound of Example 6-2 was synthesized in the manner similar to Example 6-1.

Example 6-2

Ethyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-aminobutanoate dihydrochloride

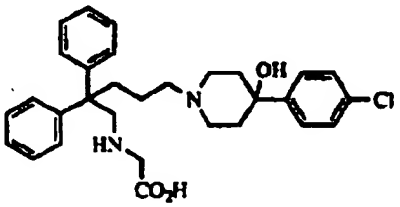


^{1}H-NMR ($CDCl_3$) δ: 1.03-1.34(5H,m), 1.35-1.77(6H,m), 2.04(2H,dt), 2.15-2.40(8H,m), 2.55(2H,t), 2.66(2H,br d), 3.21(2H,s), 4.08(2H,q), 7.12-7.34(12H,m), 7.42(2H,d).

The compounds of Examples 7-1 and 7-2 were synthesized in a manner similar to Example 5-1.

Example 7-1

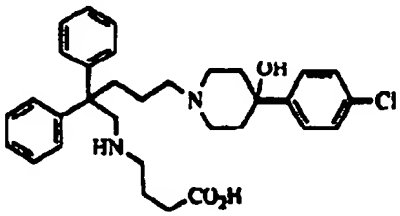
N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]glycine



^{1}H-NMR ($CDCl_3$) δ: 1.05-1.40(2H,m), 1.45-1.73(2H,m), 1.83-2.27(4H,m), 2.28-2.80(6H,m), 2.97(2H,s), 3.17(2H,s), 3.50-4.50(3H,br), 6.90-7.50(14H,m).

Example 7-2

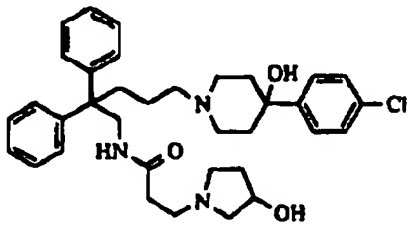
N-[5-[4-(4-Chlorophenyl)-4-hdyroxypiperidino]-2,2-diphenylpentyl]-4-aminobutyric acid



^{1}H-NMR ($CDCl_3$) δ: 1.18-1.43(2H,m), 1.52-1.83(4H,m), 2.05-2.34(7H,m), 2.40-2.80(6H,m), 2.81-3.04(2H,m), 3.28(2H,s), 4.10-4.80(2H,br), 7.08-7.50(14H,m).

Example 8-1

N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-hyroxypyrrolidin-1-yl)propanamide



1) 5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-1-(3-chloropropyonylamino)-2,2-diphenylpentane

To a solution of 1-amino-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane (0.9 g) in THF (20 ml) was added a saturated aqueous sodium hydrogen carbonate solution (20 ml) and the mixture was stirred vigorously under ice-cooling. 3-Chloropropionylchloride (0.21 ml) was added and the mixture was stirred for 2 hours. The reaction mixture was diluted with ethyl acetate and organic layer was separated, washed with pure water, and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluting with ethyl acetate-methanol (7:3) to give 5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-1-(3-chloro-propionylamino)-2,2-diphenylpentane (0.82 g) as a noncrystalline powder. ^{1}H-NMR ($CDCl_3$) δ: 1.25-1.43(2H,m), 1.63-1.75(2H,m), 2.10-2.59(10H,m), 2.75-2.97(2H,m), 3.74(2H,t), 4.05(2H,d), 5.21(1H,br s), 7.14-7.38 (12H,m), 7.43(2H,d).

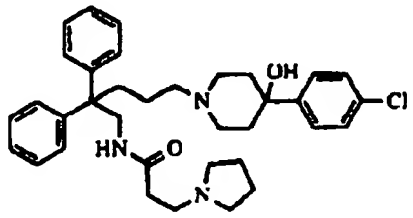
To a solution of 5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-1-(3-chloropropionylamino)-2,2-diphenylpentane (0.19 g) in ethanol were added potassium carbonate (0.10 g) and 3-hydroxypyrrolidine (0.045 ml) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was

diluted with ethyl acetate and organic layer was separated, washed with pure water, and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (1:1) to give the titled compound (0.08 g) as a noncrystalline powder. ^{1}H-NMR ($CDCl_3$) δ: 1.32-1.47(2H,m), 1.64-1.75(2H,m), 1.87-2.38 12H,m), 2.41-2.90(8H,m), 4.02-4.18(2H,m), 4.22-4.28(1H,m), 7.18-7.36(12H,m), 7.43(2H,d), 7.93(1H,br s).

The compounds of Examples 8-2 and 8-3 were synthesized in a manner similar to Example 8-1.

Example 8-2

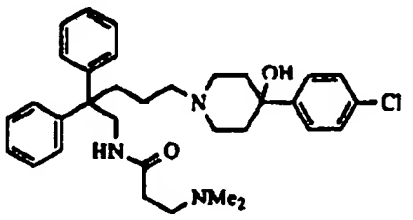
5-[4-(4-Cholophenyl)-4-hydroxypiperidino]-2,2-diphenyl-1-(3-pyrrolidin-1-yl-propionylamino)pentane



^{1}H-NMR ($CDCl_3$) δ: 1.23-1.40(2H,m), 1.49-1.72(8H,m), 1.94-2.15(4H,m), 2.22-2.37(8H,m), 2.50(2H,t), 2.65(2H,br d), 3.83(2H,d), 4.04(2H,d), 7.10-7.36(12H,m), 7.43(2H,d), 8.22(1H,br).

Example 8-3

5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1-[3-(dimethylamino)propionylamino]-2,2-diphenylpentane

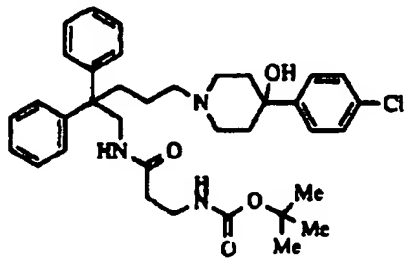


^{1}H-NMR ($CDCl_3$) δ: 1.25-1.43(2H,m), 1.52-1.79(4H,m), 1.92(6H,s), 2.03-2.52(10H,m), 2.62-2.82(2H,br),

4.03(2H,d), 7.10-7.46(14H,m), 8.22(1H,br).

Example 9

N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(t-butoxycarbonyl)aminopropanamide

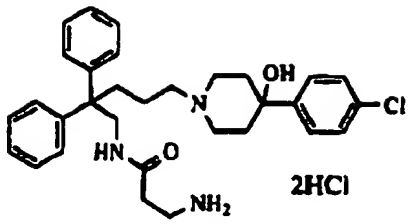


To a solution of 1-(5-amino-4,4-diphenylpentyl)-4-(4-chlorophenyl)-4-hydroxypiperidine (0.8 g) in DMF (5 ml) were added N-Boc-β-alanine (0.3 g), triethyl amine (0.56 ml), and diethylphosphoro cyanidate (0.28 ml) at 0°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into pure water (20 ml) and extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (0.85 g) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.39(2H,m), 1.47(9H,s), 1.61-1.75(2H,m), 1.98-2.16(4H,m), 2.18-2.38(10H,m), 2.67-2.81(2H,m), 3.30-3.42(2H,m), 4.01(2H,d), 5.08(1H,brs), 5.79(1H,br s), 7.16-7.35(12H,m), 7.42(2H,d).

Example 10

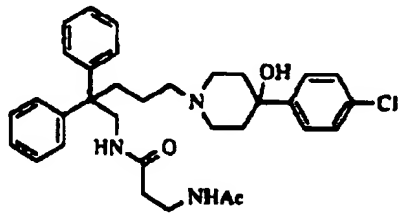
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-aminopropanamide dihydrochloride



To a solution of N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(t-butoxycarbonyl)aminopropanamide (0.8 g) in ethyl acetate (10 ml) was added 4N-hydrochloric acid-ethyl acetate solution (2.5 ml) and stirred 60°C for 3 hours. The solvent was distilled off under reduced pressure. The residue was suspended in ethyl acetate and the solid was collected by filtration to give the titled compound (0.74 g) as a noncrystalline powder.
^{1}H-NMR ($CDCl_3$) δ: 1.22-1.42(2H,m), 1.60-1.73(2H,m), 1.96-2.19(6H,m), 2.23-2.39(4H,m), 2.59-2.71(2H,m), 2.83(2H,t), 4.03(2H,d), 6.52-6.62(1H,m), 7.18-7.33(12H,m), 7.42(2H,d).

Example 11

N-[5-[4-(4-Chlorophenyl-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(acetylamino)propanamide



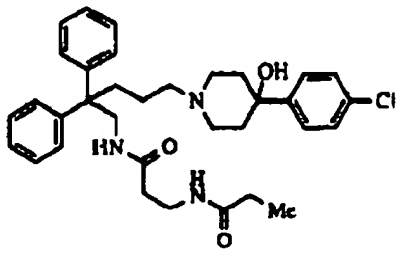
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-aminopropanamide dihydrochloride (0.16 g) was added to the mixture of THF (3 ml) and saturated aqueous sodium hydrogen carbonate solution (3 ml). Anhydrous acetic acid (0.03 ml) was added and the mixture was stirred at room temperature for 1 hour. The reaction mixture was extracted with ethyl acetate and the organic extract was washed with a saturated

aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate. The residue was crystallized from isopropylether to give the titled compound (0.07 g).

Melting point: 128°C - 130°C

Example 12

N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(propionylamino)propanamide



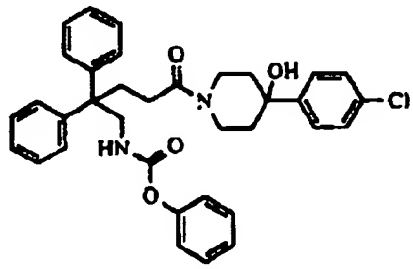
The titled compound (0.02 g) was obtained in a manner similar to Example 11.

Recrystallization solvent: isopropyl ether

Melting point: 128°C - 130°C

Example 13

1-[4,4-Diphenyl-5-(phenyloxycarbonylamino)pentanoyl]-4-(4-chlorophenyl)-4-hydroxypiperidine



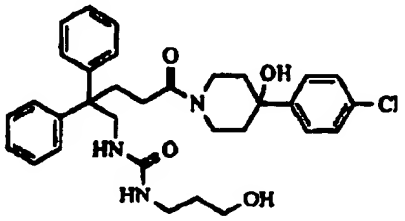
To a solution of 1-(5-amino-4,4-diphenylpentanoyl)-4-(4-chlorophenyl)-4-hydroxypiperidine (2.32 g) obtained in Reference Example 22 in THF (50 ml) were added triethylamin

(1.39 ml) and phenyl chlorocarbonat (0.69 ml) at 0°C. The reaction mixtur was stirred for 1 hour, diluted with ethyl acetate, washed with pure water, and a saturated aqueous sodium chloride solution. The organic layer was dried and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (3:7) to give the titled compound (2.90 g) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.57-2.34(8H,m), 2.56(2H,t), 2.91-3.04(2H,m), 3.25-3.50(2H,m), 3.87-4.17(2H,m), 4.43-4.57(2H,m), 4.83-4.92(2H,m), 7.00(2H,d), 7.14-7.42(12H,m).

Example 14

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenyl-5-oxopentyl]-3-[3-(hydroxy)propyl]urea



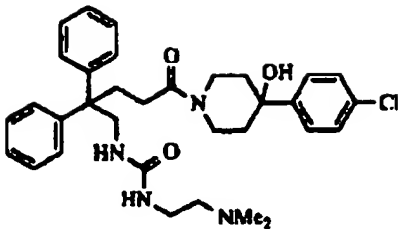
In a manner similar to Example 11, the titled compound (0.32 g) was obtained from 1-[4,4-diphenyl-5-phenyloxycarbonylamino)pentanoyl]-4-(4-chlorophenyl)-4-hydroxypiperidine (0.14 g).

Recrystallization solvent: ethyl ether

Melting point: 192°C - 194°C

Example 15

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenyl-5-oxopentyl]-3-[3-(dimethylamino)ethyl]urea



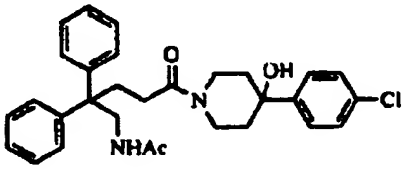
The titled compound was obtained in a similar manner to Example 11.

Recrystallization solvent: ethyl ether/ether

Melting point: 223°C - 225°C

Example 16

1-(5-Acetylamino-4,4-diphenylpentanoyl)-4-(4-chlorophenyl)-4-hydroxypiperidine

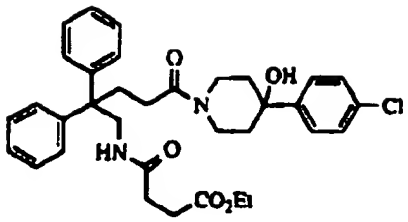


To a solution of 1-(5-amino-4,4-diphenylpentanoyl)-4-(4-chlorophenyl)-4-hydroxypiperidine (0.46 g) in THF (10 ml) were added triethylamine (0.28 ml) and anhydrous acetic acid (0.1 ml) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and washed serially with pure water and a saturated aqueous sodium chloride solution. The organic layer was dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (9:1) and crystallized from ethyl acetate-ether to give the titled compound (0.36 g).

Melting point: 191°C - 192°C

Example 17

Ethyl N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenyl-5-oxopentyl]succinamate

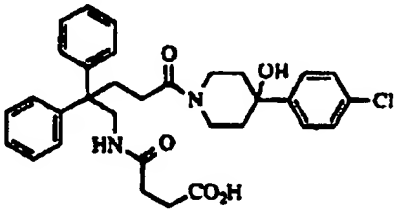


In a similar manner to Example 16, 1-(5-amino-4,4-diphenylpentanoyl)-4-(4-chlorophenyl)-4-hydroxypiperidine (0.56 g) was acylated with ethylsuccinylchloride and the desired product was crystallized from ether to give the titled compound (0.53 g).

Melting point: 94°C - 96°C

Example 18

N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenyl-5-oxopentyl]succinamic acid

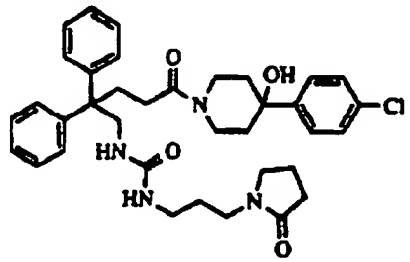


To a solution of ethyl 4-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenyl-5-oxopentyl] succinamate (0.3 g) in THF (1 ml) was added 1N-aqueous sodium hydroxide solution (1 ml) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was made acidic with 1N-hydrochloric acid and extracted with ethyl acetate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (9:1). The desired product was crystallized from ethyl acetate to give the titled compound (0.36 g).

Melting point: 177°C - 180°C

Exampl 19

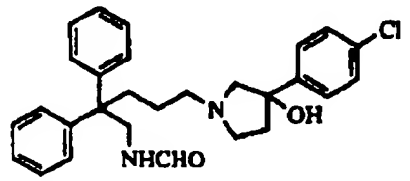
1-[5-[4-Chloroph nyl)-4-hydroxypiperidino]-2,2-diphenyl-5-oxopentyl]-3-[3-(2-oxo-1-pyrrolidino)propyl)urea



In a similar manner to Example 16, the titled compound was obtained.
Recrystallization solvent: ethyl ether
Melting point: 194°C - 197°C

Example 20

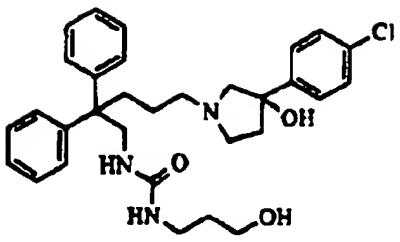
5-[3-(4-Chlorophenyl)-3-hydroxypyrrolidin-1-yl]-2,2-diphenyl-1-formylpentanamine



In a manner similar to Example 1-1, the titled compound was obtained from 3-(4-chlorophenyl)-3-hydroxypyrrolidine (described in Medicinal Chemistry Research 3, 459-467 (1993)).
^{1}H-NMR ($CDCl_3$) δ: 1.20-1.38(2H,m), 1.95(1H,br), 2.13-2.55(8H,m), 2.91(1H,d) 3.01-3.14(1H,m), 3.86-4.08(2H,m), 5.12(1H,br s), 7.16-7.44(14H,m), 8.10(1H,s).

Example 21

1-[5-[4-(4-Chlorophenyl)-3-hydroxypiperidine]-2,2-diphenylpentyl]-3-[3-hydroxy)propyl]urea



To a solution of 5-[3-(4-chlorophenyl)-3-hydroxypyrrolidin-1-yl]-2,2-diphenyl-1-formylpentanamine (0.92 g) in ethanol (5 ml) was added 4N aqueous sodium hydroxide solution (5 ml) and the mixture was stirred at 90°C for 16 hours. The reaction mixture was extracted with ethyl acetate and the extract was washed with a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure to provide the deformylated compound (0.81 g). The obtained deformylated compound (0.65 g) was dissolved in THF (15 ml), and triethylamine (0.42 ml) was added. To the resulting mixture was added phenyl chlorocarbonate (0.21 ml) at 0°C and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was extracted with ethyl acetate and the extract was washed with a saturated aqueous sodium chloride solution and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (4:1). The solvent was distilled off under reduced pressure to provide the phenyl carbamate compound as an oily residue. In a manner similar to Example 4-1, the titled compound (0.2 g) was obtained.

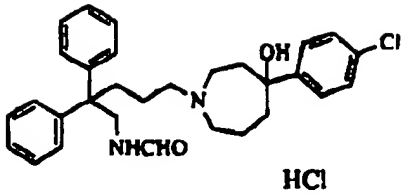
Recrystallization solvent: ether/hexane

Melting point: 150°C - 153°C

Example 22

1-Formylamino-[5-[4-hydroxy-4-(4-chlorophenyl) hexamethylenimin-1-yl]-2,2-diphenylpentane

hydrochlorid

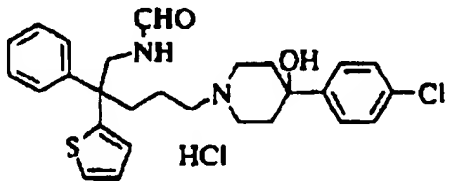


In a manner similar to Example 1-1, the titled compound was obtained from 4-(4-chlorophenyl)-4-hydroxyhexamethylenimine.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.40(2H,m), 1.50-2.23(9H,m), 2.25-2.97(6H,m), 4.06(2H,d), 5.20-5.35(1H,br), 7.05-7.42(14H,m), 8.08(1H,d).

Example 23:

5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1-formylamino-2-phenyl-2-(2-thienyl)pentane hydrochloride

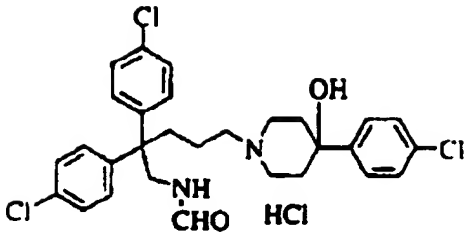


In a similar manner to Example 1-1, the titiled compound was synthesized as a noncrystalline powder from 5-formylamino-1-iodo-4-phenyl-4-(2-thienyl)pentane described in Reference Example 31.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.58(2H,m), 1.66(2H,d), 1.97-2.50(9H,m), 2.61-2.77(2H,m), 4.03(2H,dd), 5.40-5.51(1H,br), 6.83-6.99(2H,m), 7.13-7.48(10H,m), 8.08(1H,d).

Example 24:

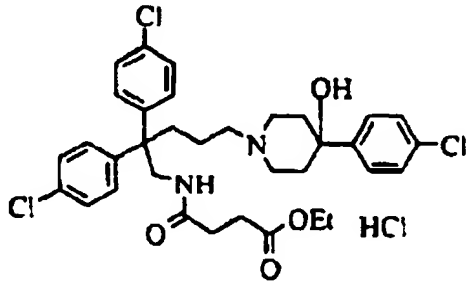
2,2-Bis(4-chlorophenyl)-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-1-formylaminopentane hydrochloride



In a similar manner to Example 1-1, the titiled compound was synthesized as a noncrystalline powder from 4,4-bis(4-chlorophenyl)-5-formylamino-pentyl-1-tosylate described in Reference Example 7-5.
^{1}H-NMR ($CDCl_3$) δ: 1.05-1.38(2H,m), 1.60-1.80(2H,m), 1.85-2.15(5H,m), 2.23-2.40(4H,m), 2.58-2.75(2H,m), 4.00(2H,d), 5.08-5.20(1H,br), 7.00-7.20(4H,m), 7.29(6H,d), 7.42(2H,d), 8.10(1H,s).

Example 25:

Ethyl N-[2,2-bis(4-chlorophenyl)-5-[4-(4-chorolophenyl)-4-hydroxypiperidino]]pentylsuccinamate hydrochloride



To a solution of 2,2-bis(4-chlorophenyl)-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-1-formylaminopentane (1.7g) in ethanol (30ml) was added 6N-aqueous sodium hydroxide solution (10ml) and the mixture was stirred at 100°C for 14 hours. The solvent was distilled off under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, respectively and dried. The solvent was distilled off under reduced pressure and 4N-hydrogen chorolide-ethyl acetate was added to give

2,2-bis(4-chl roph nyl)-5-[4-(4-chorolo-phenyl)-4-hydroxypiperidino]pentylamine dihydrochloride (1.6g) as a noncrystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.55(4H,m), 1.58-1.73(2H,m), 1.94-2.16(5H,m), 2.20-2.40(4H,m), 2.59-2.72(2H,m), 3.26(2H,s), 7.03-7.18(4H,m), 7.20-7.35(6H,m), 7.35-7.45(2H,m).

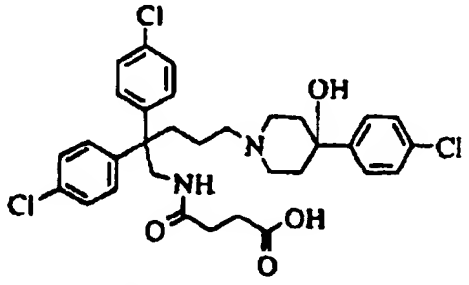
In a similar acylation in Example 3-1, the titiled compound was synthesized as a noncrystalline powder from

2,2-bis(4-chlorophenyl)-5-[4-(4-chorolophenyl)-4-hydroxypiperidino]pentylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.40(5H,m), 1.59-1.74(2H,m), 1.84-2.15(5H,m), 2.22-2.40(6H,m), 2.53-2.72(4H,m), 3.94(2H,d), 4.09(2H,q), 5.24(1H,br t), 7.05-7.20(4H,m), 7.20-7.34(6H,m), 7.42(2H,d).

Example 26:

N-[2,2-Bis(4-chlorophenyl)-5-[4-(4-chorolo-phenyl)-4-hydroxypiperidino]]pentylsuccinamic acid



By a hydrolysis described in Example 5-1, the titiled compound was synthesized as a noncrystalline powder from

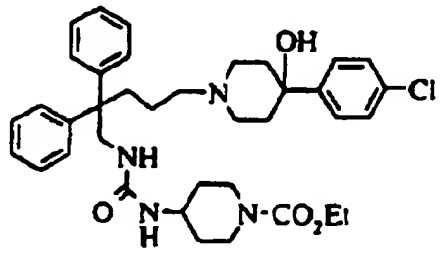
Ethyl N-[2,2-bis(4-chlorophenyl)-5-[4-(4-chorolo-phenyl)-4-hydroxypiperidino]]pentylsuccinamate.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.50(2H,m), 1.60-1.76(2H,m), 1.97-2.42(9H,m), 2.75-3.20(6H,m), 3.75-4.00(2H,m), 5.25-5.60(1H,br), 7.17(4H,d), 7.30-7.55(8H,m).

The compound 27-1 to 27-23 were synthesized in the same manner as Example 4-1.

Example 27-1:

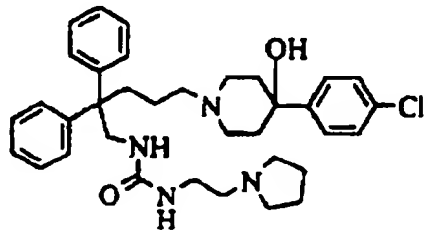
1-[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]-3-[(1-ethoxycarbonyl)piperidin-4-yl]urea



Recrystallization solvent: ethyl ether
Melting point : 223°C to 226°C

Example 27-2:

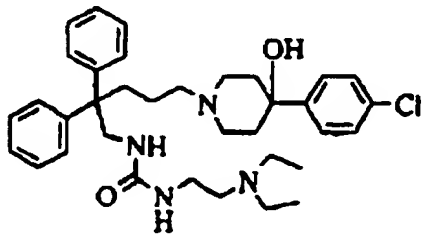
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[2-(1-pyrrolidino)ethyl]urea



Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 132°C to 133°C

Example 27-3:

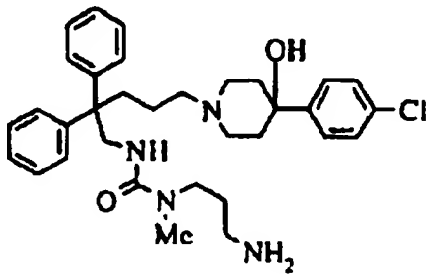
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[2-(diethylamino)ethyl]urea



Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 134°C to 136°C

Example 27-4:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-aminopropyl)-3-methylurea

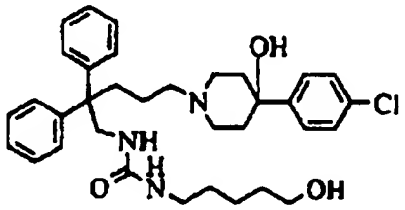


Recrystallization solvent : ethyl acetate

Melting point : 92°C to 94°C

Example 27-5:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(5-hydroxypentyl)urea

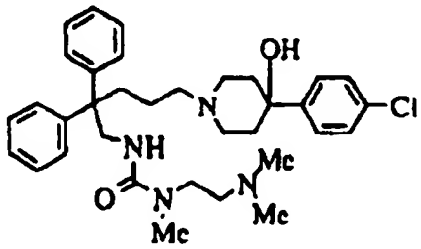


Recrystallization solvent : ethyl acetate/ethyl ether

Melting point : 149°C to 151°C

Example 27-6:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[2-(dimethylamino)ethyl]-3-methyl urea

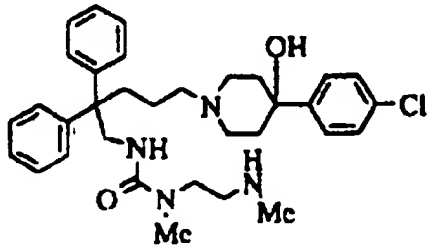


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.42(2H,m), 1.58-1.71(2H,m), 1.99(6H,s), 2.00-2.17(4H,m), 2.22-2.38(6H,m), 2.61-2.75(2H,m), 2.73(3H,s), 3.12(2H,t), 3.97(2H,d), 5.23(1H,br s), 7.17-7.33(12H,m), 7.43(2H,d).

Example 27-7:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[2-(methylamino)ethyl]-3-methylurea

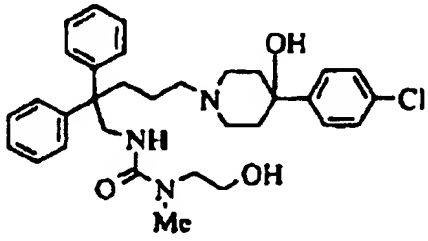


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.38(2H,m), 1.65(2H,brd), 1.95-2.42(8H,m), 2.20(3H,s), 2.53-2.78(4H,m), 2.72(3H,s), 3.12-3.24(2H,m), 3.95(2H,d), 5.20(1H,brs), 6.82-6.93(1H,m), 7.15-7.34(11H,m), 7.42(2H,d).

Example 27-8:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(2-hydroxyethyl)-3-methylurea

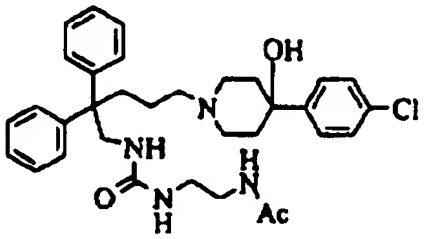


^{1}H-NMR ($CDCl_3$) δ: 1.27-1.39(2H,m), 1.67(2H,brd), 2.02-2.18(2H,m), 2.25-2.43(2H,m), 2.60-2.78(2H,m), 2.68(3H,s), 3.32(2H,t), 3.97(2H,t), 4.28(1H,brs), 6.82-6.94(1H,m), 7.16-7.34(11H,m), 7.42(2H,d).

Example 27-9:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-

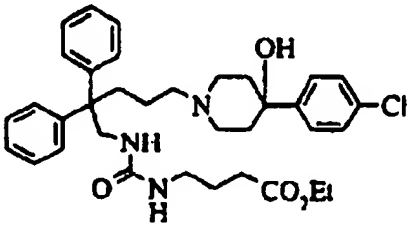
2,2-diph nylpentyl]-3-[2-(ac tylamino)ethyl]urea



Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 210°C to 213°C

Example 27-10:

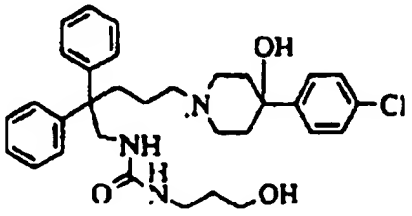
Ethyl 4-[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]ureido butyrate



Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 121°C to 123°C

Example 27-11:

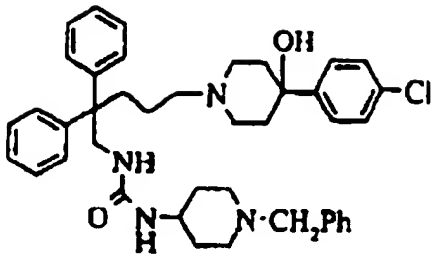
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-hydroxypropyl)urea



Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 101°C to 102°C

Example 27-12:

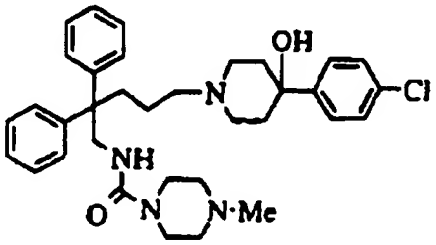
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(1-benzylpiperidin-4-yl)urea



Recrystallization solvent : isopropyl ether/ethyl ether
Melting point : 176°C to 178°C

Example 27-13:

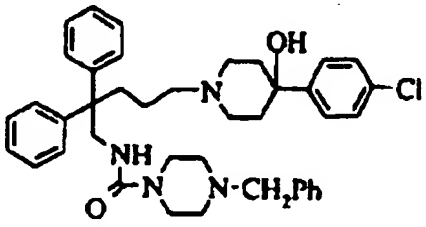
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-methylpiperadine-1-carboxamide



Recrystallization solvent : isopropyl ether/ethyl ether
Melting point : 156°C to 157°C

Example 27-14:

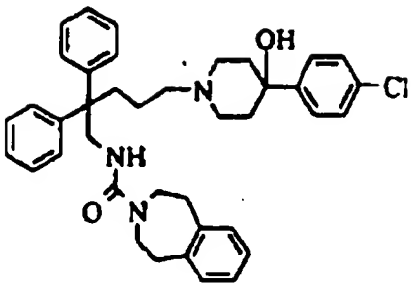
N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-benzylpiperadine-1-carboxamide



Recrystallization solvent : isopropyl ether/ethyl ether
Melting point : 142°C to 143°C

Example 27-15:

1N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-1,2,4,5-tetrahydro-3-benzazepine-3-carboxamide

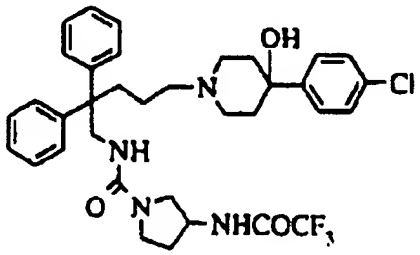


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.23-1.44(2H,m), 1.57-1.80(2H,m), 1.98-2.20(4H,m), 2.23-2.47(4H,m), 2.62-2.82(6H,m), 3.32-3.37(4H,m), 3.97-4.06(3H,m), 7.02-7.19(4H,m), 7.21-7.43(14H,m).

Example 27-16:

1N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(trifluoroacetylamino)pyrrolidine-1-carboxamide

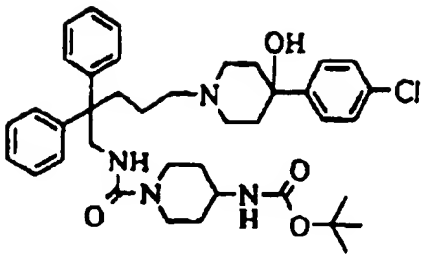


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.30(2H,br), 1.61-1.75(2H,m), 1.96-2.42(11H,m), 2.70(2H,br), 3.12-3.24(2H,m), 3.27-3.48(2H,m), 3.72-3.80(1H,m), 3.83-4.07(2H,m), 4.42(1H,br), 7.17-7.42(14H,m).

Example 27-17:

1N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-(t-butoxycarboxamido)piperidine-1-carboxamide

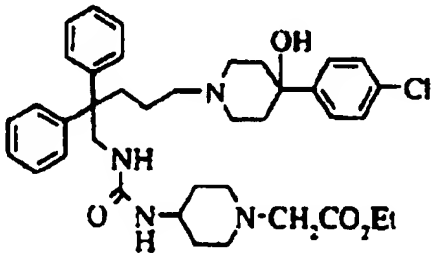


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.37(2H,m), 1.43(9H,s), 1.60-1.91(6H,m), 1.97-2.16(4H,m), 2.22-2.39(4H,m), 2.57-2.79(4H,m), 3.43-3.65(3H,m), 3.95(3H,br), 4.42(1H,br), 7.15-7.37(12H,m), 7.40-7.45(2H,m).

Example 27-18:

Ethyl [4-[3-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]ureido]piperidino] acetate

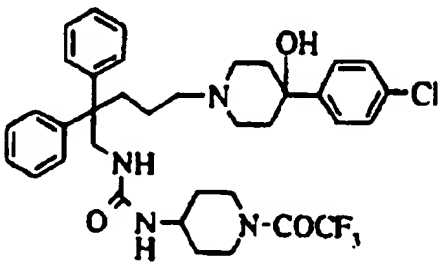


Recrystallization solvent : isopropyl ether/ethyl ether

Melting point : 116°C to 118°C

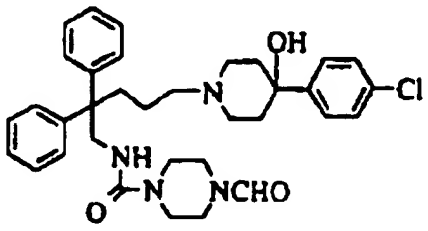
Example 27-19:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[1-(trifluoroacetyl)piperidin-4-yl]urea



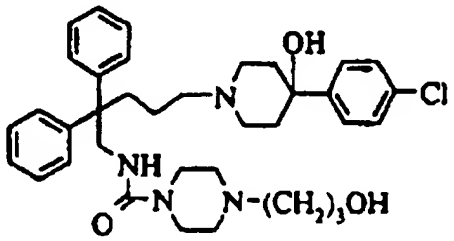
Recrystallization solvent : ethyl ether
Melting point : 192°C to 193°C
Example 27-20:

1N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-formyl-1-piperadzinecarboxamide



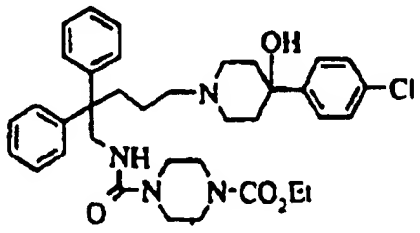
Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 191°C to 192°C
Example 27-21:

1N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-(3-hydroxypropyl)-1-piperadzine-carboxamide



Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 125°C to 127°C
Example 27-22:

1N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-(ethoxycarbonyl)-1-piperadine-carboxamide

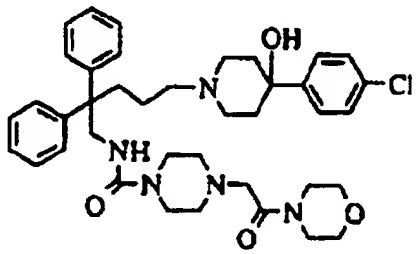


Noncrystalline powd r

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.37(2H,m), 1.25(3H,t), 1.61-1.68(2H,m), 1.97-2.17(4H,m), 2.21-2.38(4H,m), 2.60-2.72(2H,m), 3.03-3.20(4H,m), 3.34-3.41(4H,m), 3.92-4.00(1H,br), 3.96(2H,s), 4.12(2H,q), 7.17-7.44(14H).

Example 27-23:

1N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-4-(morpholinocarbonylmethyl)-1-piperadinecarboxamide



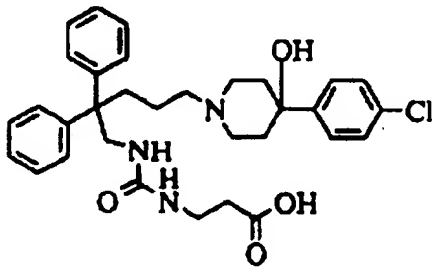
Recrystallization solvent : ethyl acetate/ethyl ether

Melting point : 163°C to 165°C

The compound 28-1 and 28-2 were synthesized in the same manner as Example 5-1.

Example 28-1:

3-[3-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]ureido]propionic acid

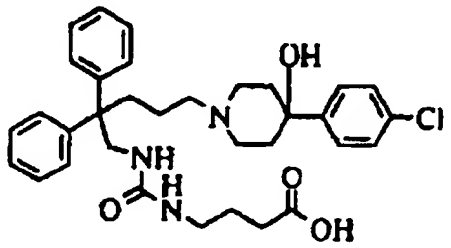


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.46(2H,br), 1.71(2H,brd), 2.17-2.60(6H,m), 2.72-3.03(4H,m), 3.15-3.45(4H,m), 3.92(2H,brd), 4.87(1H,br), 5.71(1H,br), 7.12-7.45(14H,m).

Example 28-2:

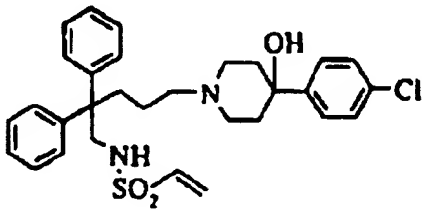
4-[3-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]ureido]butyric acid



Recrystallization solvent : water
Melting point : 137°C to 139°C

Example 29:

1N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]vinylsulfonamide



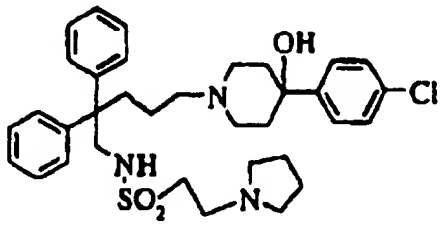
To a solution of 1-amino-5-[4-(4-chlorophenyl)-4-hydroxypiepridino]-2,2-diphenylpentane (0.9g) in THF (20ml) were added triethylamine (0.84ml) and 2-chloroethanesulfonylchloride (0.21ml) at room-temperature. The reaction mixture was stirred for 2 hours, diluted with ethyl acetate, washed with pure water, and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (7:3) to give the titled compound as noncrystalline powder (0.82g).

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.35(2H,m), 1.60-1.73(2H,m), 2.07-2.45(8H,m), 2.65-2.79(2H,m), 3.70(2H,br s), 5.55(1H,dd), 6.11(1H,d), 6.12(1H,d), 7.14-7.48(14H,m).

Example 30:

1N-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-

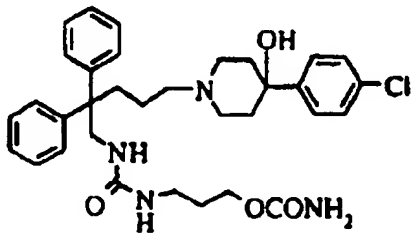
2,2-diph nylpentyl]-2-(pyrrolidino) thylsulfonamid



To a solution of 1N-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]vinylsulfonamide in ethanol was added pyrrolidine (0.062ml) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (7:3) to give the titled compound (0.10g).
Recrystallization solvent : ethyl acetate/ethyl ether
Melting point : 140°C to 142°C

Example 31:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[3-carbamoyloxy)propyl]urea

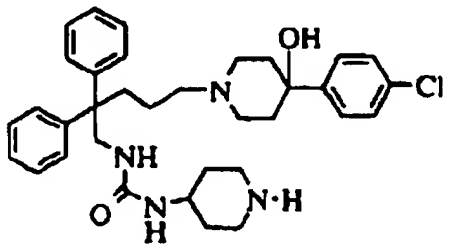


To a solution of 1-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(3-hydroxypropyl)urea described in Example 27-11 in THF (5ml) was added chlorosulfonylisocyanate (0.044ml) and the mixture was stirred at room temperature for 2 hours, followed by saturated aqueous sodium hydrogen carbonate (5ml) was added. After stirring f r 1 hour, at 45°C.

The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous s dium chloride, and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (4:1) to give the titled compound (0.10g).
Recrystallization solvent : ethyl ether
Melting point : 152°C to 154°C

Example 32:

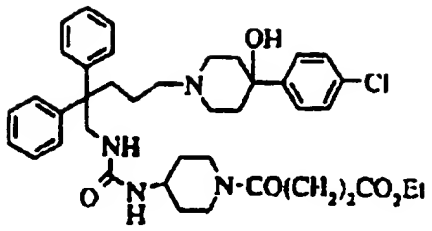
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(piperidin-4-yl)urea



To a solution of 1-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[1-(trifluoroacetyl)piperidin-4-yl]urea (2.35g) described in Example 27-19 in THF (10.5ml) was added 0.5N-sodium hydroxide solution (10.5ml) and the mixture was stirred for 2 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium chloride, and dried. The solvent was distilled off under reduced pressure. The residue was crystallized from ethyl acetate-ether (4:1) to give the titled compound (1.92 g).
Melting point : 194°C to 196°C

Example 33-1:

Ethyl 4-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino] piperidino-4-oxobutyrate



To a mixture of 1-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(piperidin-4-yl)urea described in Example 32 in THF (10ml) and triethylamine (0.21ml) was added ethyl succinylchloride (0.077ml). After stirring for 2 hours at room temperature, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (4:1) to give the titled compound (0.28g).

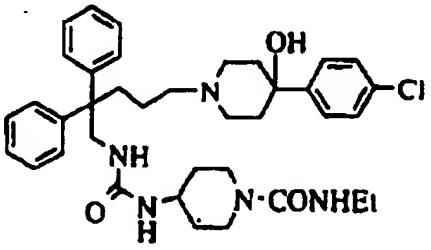
Recrystallization solvent : ethyl acetate/ethyl ether

Melting point : 173°C to 175°C

The compound 33-2 to 33-5 were synthesized in the same manner as Example 33-1.

Example 33-2:

N-Ethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino-1-piperidinecarboxamide

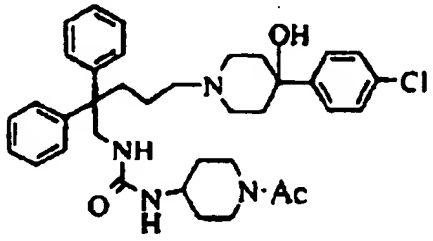


Recrystallization solvent : ethyl acetate/ethyl ether

Melting point : 193°C to 195°C

Example 33-3:

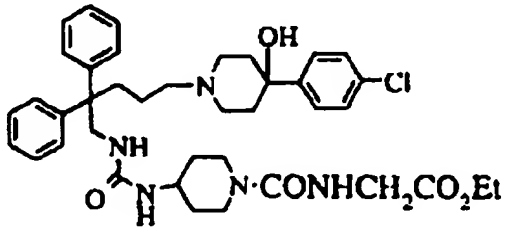
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(1-acetylpiperidin-4-yl)urea



Recrystallization solvent : ethyl ether
Melting point : 146°C to 148°C

Example 33-4:

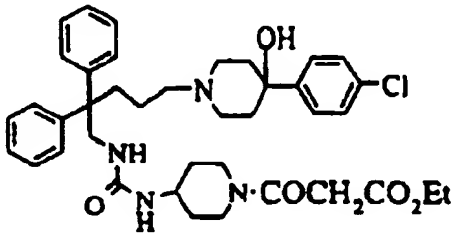
N-Ethoxycarbonylmethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]aminocarbonylamino-1-piperidinecarboxamide



Recrystallization solvent : ethyl ether
Melting point : 220°C to 221°C

Example 33-5:

Ethyl 3-[4-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]aminocarbonylamino]piperidino-3-oxopropionate

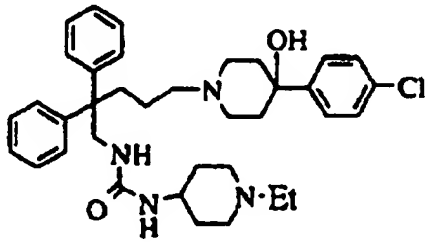


Recrystallization solvent : ethyl ether

Melting point : 173°C to 175°C

Example 34-1:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(1-ethylpiperidin-4-yl)urea



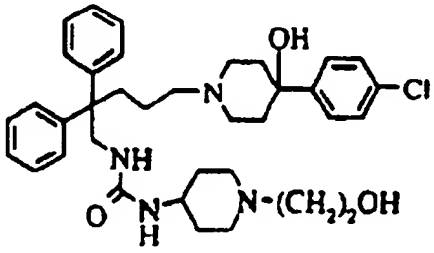
To a mixture of 1-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(piperidin-4-yl)urea (0.29g) described in Example 32 in DMF (5ml) and potassium carbonate (0.14g) was added ethyl iodide (0.12ml). After stirring for 8 hours at room temperature, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium chloride solution, and dried. The solvent was distilled off under reduced pressure. The residue was crystallized from ethyl acetate to give the titled compound (0.14g).

Melting point : 154°C to 157°C

The compound 34-2 to 34-4 were synthesized in the same manner as Example 34-1.

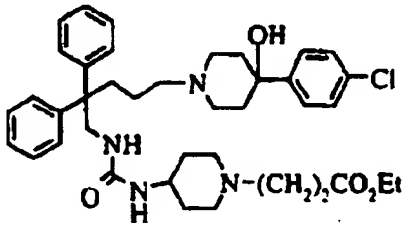
Example 34-2:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[1-(2-hydroxyethyl)piperidin-4-yl]urea



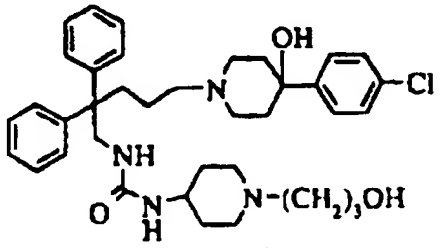
Recrystallization solvent : thyl eth r
Melting point : 177°C to 180°C
Example 34-3:

Ethyl 3-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino piperidino]propionate



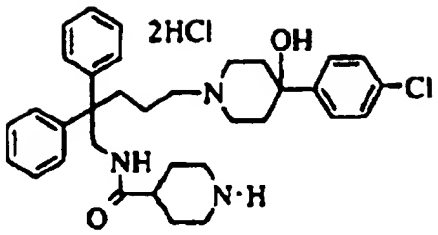
Recrystallization solvent : ethyl ether/ethyl ether
Melting point : 148°C to 151°C
Example 34-4:

1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-[1-(3-hydroxypropyl)piperidin-4-yl]urea



Recrystallization solvent : ethyl ether/ethyl ether
Melting point : 194°C to 197°C
Example 35:

1-[(Piperidin-4-yl)carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane dihydrochloride



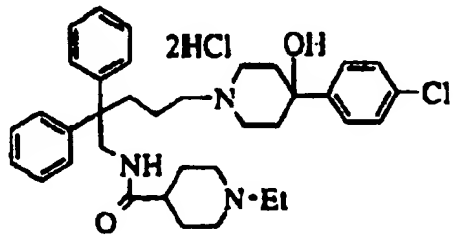
To a mixture of 1-trifluoroacetylpiperidin-4-carboxylic acid (1.2 g) in acetonitrile (30 ml) and triethylamine (0.6 g) was added cloroisopropylcarbonate (0.67 g) slowly and the mixture was stirred for 2 minutes at -15°C. A solution of 1-amino-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane (2.5 g) and triethylamine (0.5 g) in THF (50 ml) was added to the mixture and the mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and water, and dried. The solvent was distilled off under reduced pressure. The residue was disolved in ethanol-water (2:1), followed by sodium hydroxide (2 g) was added to the mixture. The mixture was stirred at room temperature for 18 hours. The reaction mixture was distilled off under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate, washed, and dried. The solvent was distilled off under reduced pressure and the residue was purified by alumina column eluting with ethyl acetate-ethanol (4:1). The eluted solution was distilled off and the residue was disolved in ethyl acetate. To the solution was added an excess amount of 4N-hydrocloric acid/ethyl acetate and the solvent was distilled off under reduced pressure to give the titled compound.

Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.70(9H,m), 1.87-2.18(6H,m), 2.20-2.39(4H,m), 2.42-2.70(4H,m), 3.05(2H,dt), 3.98(2H,d), 5.02(1H,t), 7.14-7.48(14H,m).

Example 36-1:

1-[(N-Ethylpiperidin-4-yl)carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane dihydrochloride



To a solution of 1-[(Piperidin-4-yl)carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane (0.4g) in acetonitrile (10ml) were added potassium carbonate (0.5g) and ethyl iodide (0.2ml) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was disolved in ethyl acetate, washed with water, and dried. The solvent was distilled off under reduced pressure. The residue was purified by aluminum oxide column eluting with ethyl acetate. The eluted solution was distilled off and the residue was disolved in ethyl acetate. An excess amount of 4N-hydrocloric acid/ethyl acetate was added to the solution and the solvent distilled off under reduced pressure to give the titled compound.

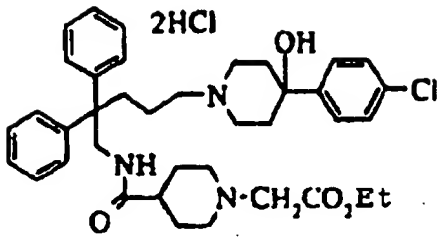
Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.05(3H,t), 1.20-1.85(14H,m), 1.80-2.35(8H,m), 2.65(2H,m), 2.90(2H,m), 3.99(2H,d), 5.04(1H,t), 7.14-7.48(14H,m).

The compound 36-2 to 36-4 were synthesized in the same manner as Example 36-1.

Example 36-2:

1-[N-(Ethoxycarbonylmethyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane dihydrochloride

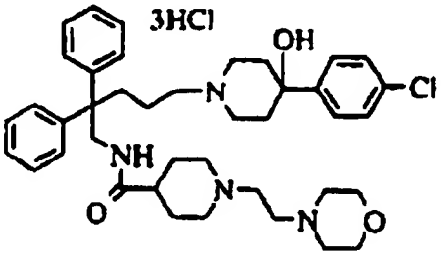


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t), 1.20-1.85(10H,m), 1.80-2.40(8H,m), 2.65(2H,m), 2.90(2H,m), 3.16(2H,s), 3.98(2H,d), 4.16(2H,q), 5.04(1H,t), 7.14-7.48(14H,m).

Example 36-3:

1-[[N-(2-Morpholinoethyl)piperidin-4-yl] carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino] -2,2-diphenylpentane trihydrochloride

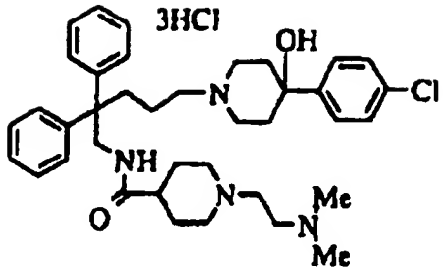


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.85(12H,m), 1.80-2.50(12H,m), 2.46(4H,s), 2.65(2H,m), 2.90(2H,m), 3.70(4H,m), 3.98(2H,d), 5.01(1H,t), 7.14-7.48(14H,m).

Example 36-4:

1-[[N-(2-Dimethylaminoethyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentane trihydrochloride



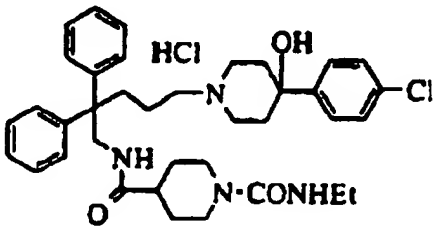
Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.85(12H,m), 2.12(6H,s), 2.40(4H,s), 1.80-2.50(12H,m), 2.65(2H,m), 2.89(2H,m), 3.98(2H,d), 5.02(1H,t), 7.14-7.48(14H,m).

The compound 37-1 to 37-8 were synthesized in the same manner as Example 33-1.

Example 37-1:

1-[[(N-Ethylcarbamoyl)piperidin-4-yl]carboamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride

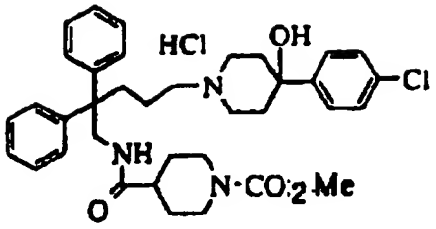


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.12(3H,t), 1.10-2.10(14H,m), 2.20-2.40(4H,m), 2.45-2.95(4H,m), 3.20(2H,m), 3.85-3.91(2H,m), 4.00(2H,d), 4.38(1H,t), 5.02(1H,t), 7.14-7.48(14H,m).

Example 37-2:

1-[[(N-Methylcarbamoyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride

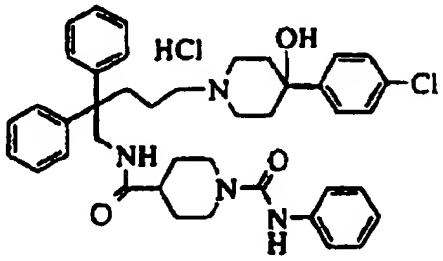


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.80(8H,m), 1.90-2.15(4H,m), 2.20-2.40(4H,m), 2.60-2.85(4H,m), 3.67(3H,s), 3.95-4.20(2H,d), 4.00(2H,d), 4.38(1H,t), 5.02(1H,t), 7.14-7.48(14H,m).

Example 37-3:

1-[[(N-Phenylcarbamoyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride

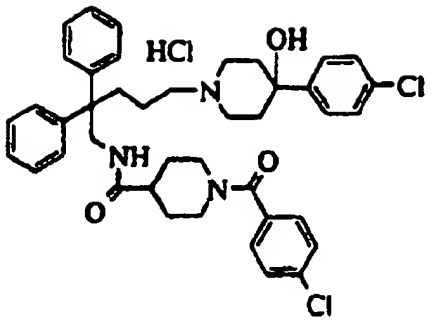


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.10-2.10(14H,m), 2.20-2.40(4H,m), 2.50-2.90(4H,m), 4.00(2H,d), 4.00-4.20(2H,m), 5.04(1H,t), 6.43(1H,m), 7.14-7.48(19H,m).

Example 37-4:

1-[[N-(4-Chlorobenzoyl)piperidin-4-yl]carboamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride

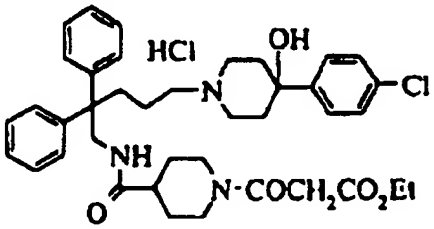


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.10-2.40(14H,m), 2.50-2.90(5H,m), 3.75(1H,m), 3.98(2H,d), 3.90-4.20(2H,m), 4.50(1H,m), 5.04(1H,t), 7.14-7.48(17H,m), 7.93(2H,d).

Example 37-5:

1-[[N-(Ethoxycarbonylacetyl)piperidin-4-yl] carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino] -2,2-diphenylpentane hydrochloride

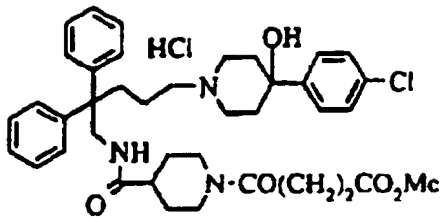


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t), 1.10-2.30(15H,m), 2.42-2.80(4H,m), 3.00(1H,t), 3.43(2H,s), 3.60(1H,m), 3.98(2H,d), 3.80-4.00(2H,m), 4.19(2H,q), 4.43(1H,m), 5.04(1H,t), 7.10-7.58(14H,m).

Example 37-6:

1-[[N-(3-Methoxycarbonylpropionyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride

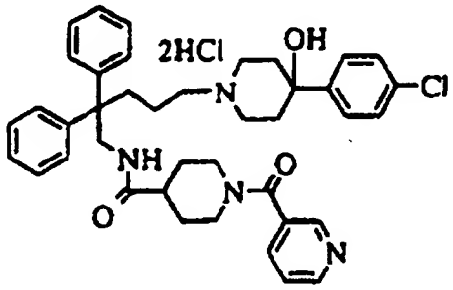


Moncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.80(10H,m), 1.90-2.50(8H,m), 2.59(4H,m), 2.60-2.80(2H,m), 2.96(1H,t), 3.68(3H,s), 3.80-4.00(4H,m), 4.40(1H,d), 5.18(1H,m), 7.00-7.50(14H,m).

Example 37-7:

1-[[N-(Nicotinoyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane dihydrochloride

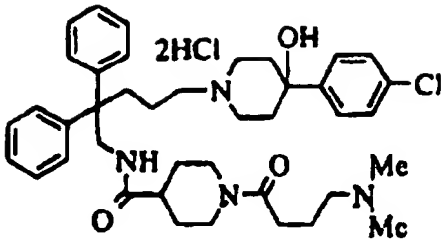


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.80(10H,m), 1.90-2.50(8H,m), 2.60(2H,m), 2.80-3.10(2H,m), 3.70(1H,m), 4.02(2H,d), 4.50(1H,m), 5.04(1H,m), 7.00-7.50(15H,m), 7.73(1H,dt), 8.61(1H,d), 8.66(1H,dd).

Example 37-8:

1-[[N-(4-Dimethylaminobutylyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane dihydrochloride

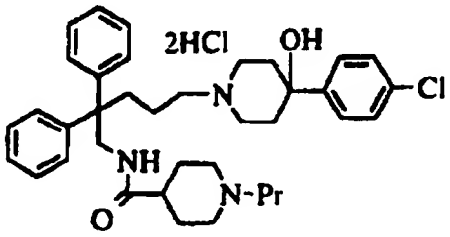


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.80(10H,m), 2.16(6H,s), 1.90-2.50(15H,m), 2.60(2H,m), 2.80-3.10(1H,m), 3.70-3.90(1H,m), 4.01(2H,m), 4.50(1H,d), 5.04(1H,t), 7.00-7.50(14H,m).

Example 38:

1-[(N-Propylpiperidin-4-yl)carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane dihydrochloride



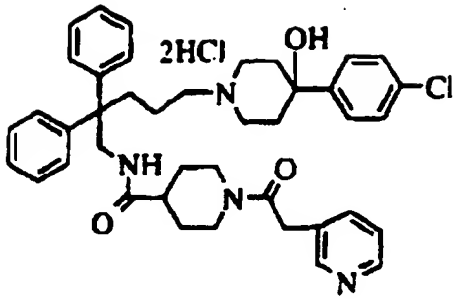
Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 0.86(3H,t), 1.20-1.85(16H,m), 1.80-2.35(8H,m), 2.64(2H,m), 2.87(2H,m), 3.98(2H,d), 5.05(1H,t), 7.14-7.48(14H,m).

The compound 39 and 40 was synthesized in the same manner as Example 37-1.

Example 39:

1-[[N-(3-Pyridylacetyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane dihydrochloride

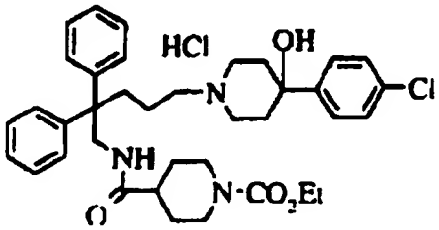


Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.80(8H,m), 1.90-2.40(8H,m), 2.60(2H,m), 2.80(3H,m), 3.04(1H,m), 3.68(2H,s), 3.80-4.00(2H,m), 4.00(2H,d), 4.48(1H,m), 5.04(1H,m), 7.00-7.50(15H,m), 7.65(1H,d), 8.54(2H,d).

Example 40

1-[[(N-Ethylcarbamoyl)piperidin-4-yl]carboxamide]5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane hydrochloride



Noncrystalline powder

^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t), 1.10-1.80(8H,m), 1.90-2.15(4H,m), 2.20-2.40(4H,m), 2.60-2.85(4H,m), 3.05(1H,m), 3.75(1H,m), 3.95-4.20(2H,d), 4.22(2H,q), 4.47(1H,t), 5.07(1H,t), 7.14-7.48(14H,m).

Formulation Example 1

(1)	Compound of Example 4-2	10.0 g
(2)	Lactose	60.0 g
(3)	Corn starch	35.0 g
(4)	Gelatin	3.0 g
(5)	Magnesium stearate	2.0 g

Using 30 ml of an 10 weight% aqueous solution of gelatin (3.0 g as g latin), a mixture of 10.0 g of the

compound obtained in Exampl 4-2, 60.0 g of lactose and 35.0 g of corn starch was granulated by m ans of a 1 mm-mesh sieve, dried at 40°C, and re-sieved. The granules thus prepared were mixed with 2.0 g of magnesium stearate and the mixture was compressed. The core tablets thus obtained were coated using an aqueous suspension containing sucrose, titanium dioxide, talc and gum arabic. The coated tablet were then glazed with beenwax to provide 1000 finished tablets.

Formulation Example 2

(1)	Compound of Example 4-2	10.0 g
(2)	Lactose	70.0 g
(3)	Corn starch	50.0 g
(4)	Soluble starch	7.0 g
(5)	Magnesium stearate	2.0 g

Using 70 ml of an aqueous solution of soluble starch (7.0 g as soluble starch), a mixture of 10.0 g of Compound obtained in Example 4-2 and 3.0 g of magnesium stearate was granulated, dried, and mixed with 70.0 g of lactose and 50.0 g of corn starch. The whole mixture was then compressed to provide 1000 tablets.

Test Example 1

Determination of inhibitory activity of ^{125}I-RANTES binding using human MIP-1α/RANTES receptor-expressing CHO cells (CHO (CCR) cells)

CHO (CCR) cells were inoculated on 96 well microplates (CulturPlate, manufactured by Packard Instrument Company, Meriden, CT. U.S.A.) in an amount of 5 x 10^4/100 µl/well and then cultured for 24 hours. After removing the medium, 35 µl/well of DMEM/0.5% BSA, 5 µl/well of a test compound diluted with DMEM/0.5% BSA and 10 µl/well of ^{125}I-RANTES (final concentration of 200 pM) were added in order, followed by incubation at room temperature for 40 minutes. Then, the cells were washed twice with 200 µl/w ll of PBS and 25 µl/well of

ethanol was added and th mixture was stirred. Furthermor , 200 µl/well of a scintillator (MicroScint-20, by Packard Instrument Company) was added and stirred, and then the radioactivity of ^{125}I-RANTES bound to the cells was measured using a TopCount (Packard Instrument Company). Assuming that the amount of binding in case that no test compound is added is 100 % and the amount bound to the CHO cells to which vector plasmid pAKKO-111H has been transfected is 0%, the concentration at which 50% inhibition of binding of ^{125}I-RANTES arises (IC_{50} value) was determined.

Compound No.	Binding inhibitory activity toward human RANTES receptor IC_{50} (µM)	Binding inhibitory activity toward human MIP-1α receptor IC_{50} (µM)
Example 1-1	0.04	0.2
Example 1-9	0.2	
Example 3-4	0.01	
Example 3-5	0.04	
Example 4-2	0.02	0.05
Example 4-3	0.01	
Example 4-5	0.02	
Example 4-7	0.04	
Example 4-8	0.05	
Example 32	0.006	5
Example 33-2	0.02	0.6
Example 33-5	0.01	3
Example 34-1	<0.01	
Example 35	0.03	5
Example 37-1	0.03	0.1
Example 37-5	0.03	0.1
Example 37-6	0.05	0.09
Ioperamide	3	

Test Example 2

Determination of inhibition activity of compound by migratrion assay using CHO (CCR) cells

Using a 96 well microchemotaxis chamber (NeuroProbe, Inc., Cabin John, MD, U.S.A), migration assay was conducted. A pretreatment was conducted by dipping a polycarbonate frame filter (NeuroProbe) having a pore size of 5 μm in a bovine fibronectin solution (10 μg/ml) diluted with PBS at room temperature for 10 minutes, followed by air-drying. A solution prepared by dissolving 40 nM RANTES (37 μl) in DMEM/0.5% BSA was added to the lower chamber. A solution (100 μl) prepared by diluting the test compound with DMEM/0.5% BSA was firstly added to the upper chamber and then CHO (CCR) cells (2×10^6 cells/ml, 100 μl) were added. After incubating at 37°C for 4 hours, the absorbance at 595 nm the CHO cells which migrated to the bottom surface of the filter was fixed and stained with Diff-Quick, and was measured. Assuming that the absorbance in case that 40 nM RANTES is added to the lower chamber and no test compound is added to the upper chamber is 100 % and the absorbance in case that only DMEM/0.5% BSA is added to the lower chamber and no test compound is added to the upper chamber is 0%, the concentration at which 50% inhibition of wandering of the CHO (CCR) cells arises (IC_{50} value) was determined.

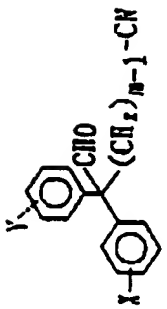
The respective test compounds inhibited migration of the CHO (CCR) cells in the IC_{50} value of less than 10 μM.

INDUSTRIAL APPLICABILITY

The present invention provides an excellent MIP-1α/RANTES-receptor antagonist useful as prophylactic and therapeutic agent for allergic and inflammatory diseases, etc., which comprises a diphenylmethane derivative or pharmaceutically acceptable salt ther f.

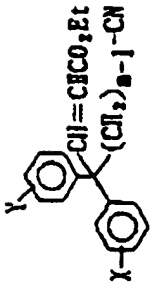
Japan s Patent Application No.343905/1995 filed December 28, 1995 and Japan se Patent Application No. 187375/1996 filed July 17, 1996, which are the priority documents of the present application, are hereby incorporated by reference in their entirety.

Table 1



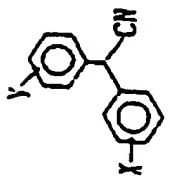
Reference Example No.	X	Y	n	^{1}H-NMR (δ_{ppm}, $CDCl_3$)
1-1	H	H	2	3.24 (2H, s), 7.19-7.50 (10H, m), 9.79(1H, s)
1-2	H	H	3	2.04-2.13 (2H, m), 2.64-2.74(2H, m), 7.11-7.45 (10H, m), 9.79(1H, s)

Table 2



Reference Example No.	X	Y	n	^{1}H-NMR (δ ppm, CDCl$_3$)
2-1	H	H	2	1.29 (3H, t), 3.23 (2H, s), 4.21 (2H, q), 5.71, 7.52 (1H each, d), 7.14-7.41(10H, m)
2-2	H	H	3	1.29 (3H, t), 2.09-2.18 (2H, m), 2.65-2.77 (2H, m), 4.20 (2H, q), 5.63, 7.47(1H each, d), 7.09-7.19 (4H, m), 7.22-7.40 (6H, m)

Table 3

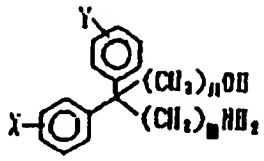


Reference Example No.	X	Y	^{1}H-NMR (δ_{ppm}, $CDCl_3$)
3-1	4-Cl	H	5.11 (1H, s), 7.23-7.42 (9H, m)
3-2	4-MeO	H	3.80 (3H, s), 5.10 (1H, s), 6.85-6.94 (2H, m), 7.20-7.40 (7H, m)
3-3	4-Cl	4-Cl	6.10 (1H, s), 7.20-7.40 (8H, m)

Table 4

Reference Example No.	X	Y	n	m	^{1}H-NMR (δ_{ppm}, $CDCl_3$)
4-1	H	H	1	3	1.23 (3H, t), 2.40-2.51 (2H, m), 2.71-2.82 (2H, m), 4.11 (2H, q), 7.26-7.43 (10H, m)
4-2	4-Cl	H	1	3	1.23 (3H, t), 2.38-2.48 (2H, m), 2.78-2.88 (2H, m), 4.10 (2H, q), 7.29-7.40 (9H, m)
4-3	4-MeO	H	1	3	1.60-1.85 (2H, m), 2.23-2.50 (2H, m), 3.69 (2H, t), 3.79 (3H, s), 6.88-6.90 (2H, m), 7.10-7.40(7H, m)
4-4	4-Cl	4-Cl	1	3	1.23 (3H, t), 2.41 (2H, m), 2.70 (2H, m), 4.10 (2H, q), 7.20-7.40 (8H, m)
4-5	H	H	1	4	1.24 (3H, t), 1.60-1.86 (2H, m), 2.38 (2H, t), 2.38-2.48 (2H, m), 4.12 (2H, q), 7.23-7.43 (10H, m)
4-6	H	H	2	3	1.21 (3H, t), 2.09, 2.66 (2H each, t), 3.03 (2H, s), 4.06 (2H, q), 7.16-7.39 (10H, m)
4-7	H	H	3	3	1.22 (3H, t), 1.95-2.06 (4H, m), 2.36-2.48 (4H, m), 4.07 (2H, q), 7.09-7.37 (10H, m)

Table 5



Reference Example No.	X	Y	m	n	m.p.(℃)	^{1}H-NMR (δ_{ppm}, $CDCl_3$)
5-1	H	H	1	3	Syrup	
5-2	4-Cl	H	1	3	Syrup	1.17-1.33 (2H, m), 1.55 (2H, br s), 2.14-2.44 (2H, m), 3.31 (2H, s), 3.56 (2H, t), 7.07-7.38 (9H, m)
5-3	4-MeO	H	1	3	Syrup	1.20-1.35 (2H, m), 2.15-2.25 (2H, m), 3.31 (2H, s), 3.57 (2H, t), 3.79 (3H, s), 6.78-6.85 (2H, m), 7.05-7.35 (7H, m)
5-4	4-Cl	4-Cl	1	3	Syrup	1.10-1.30 (2H, m), 1.55 (2H, br s), 2.14-2.24 (2H, m), 3.29 (2H, s), 3.55 (2H, t), 7.00-7.30 (8H, m)
5-5	H	H	1	4	Syrup	1.01-1.18 (2H, m), 1.42-1.65 (4H, m), 2.09-2.20 (2H, m), 3.33 (2H, s), 3.56 (2H, t), 7.12-7.35 (10H, m)
5-6	H	H	2	3	Syrup	1.14-1.32 (2H, m), 2.10-2.26 (2H, m), 2.24-2.39 (2H, m), 2.37-2.51 (2H, m), 3.15 (3H, s), 3.51 (2H, t), 7.07-7.30 (10H, m)
5-7	H	H	3	3	Syrup	1.10-1.31 (4H, m), 2.05-2.22 (4H, m), 2.66, 3.53 (2H each, t), 3.01 (3H, br s), 7.06-7.30 (10H, m)

Table 6

Reference Example No.	X	Y	R	m	n	m.p. (℃)	^{1}H-NMR (δ ppm, $CDCl_3$)
6-1	H	H	CHO	1	3	151-152	1.32 (2H, m), 2.16 (2H, m), 3.55 (2H, t), 4.05 (2H, d), 5.10-5.30 (1H, m), 7.10-7.40 (10H, m), 8.08 (1H, d)
6-2	4-Cl	H	CHO	1	3	150-161	1.00-1.23 (2H, m), 2.03 (2H, t), 3.30 (2H, q), 3.88 (2H, dd), 4.33 (1H, t), 7.10-7.37 (9H, m), 7.48 (1H, br t), 7.87 (1H, d)
6-3	4-MeO	H	CHO	1	3	Syrup	1.20-1.40 (2H, m), 2.08-2.20 (2H, m), 3.54 (2H, br t), 3.79 (3H, s), 4.01 (2H, dt), 5.20-5.30 (1H, br s), 6.80-6.88 (2H, m), 7.00-7.35 (7H, m), 8.07 (1H, d)
6-4	4-Cl	4-Cl	CHO	1	3	175-178	1.00-1.20 (2H, m), 2.04 (2H, t), 3.30 (2H, q), 3.86 (2H, d), 4.34 (1H, t), 7.10-7.40 (8H, m), 7.55 (1H, br t), 7.88 (1H, d)
6-5	H	H	CHO	1	4	Syrup	1.04-1.22 (2H, m), 1.40-1.56 (2H, m), 1.90-2.18 (2H, m), 3.54 (2H, t), 4.06 (2H, d), 5.20 (1H, br t), 7.10-7.37 (10H, m), 8.08 (1H, d)
6-6	H	H	CHO	2	3	Syrup	1.20-1.38 (2H, m), 2.20-2.40 (4H, m), 3.06 (2H, q), 3.57 (2H, t), 5.49 (1H, br), 7.10-7.34 (10H, m), 7.99 (1H, d)
6-7	H	H	Ac	3	3	Syrup	1.12-1.30 (4H, m), 1.90 (3H, s), 2.02-2.21 (5H, m), 3.15 (2H, q), 3.55 (2H, t), 5.49 (1H, br t), 7.11-7.30 (10H, m)

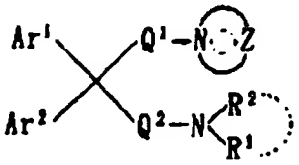
Table 7

Reference Example No.	X	Y	R	L	m	n	m.p. (℃)	^{1}H-NMR (δ, CDCl$_3$)
7-1	H	H	CHO	C	1	3	Syrup	1.49-1.65 (2H, m), 2.12-2.25 (2H, m), 3.10 (2H, t), 4.04 (2H, d), 5.07 (1H, br t), 7.11-7.40 (10H, m), 8.11 (1H, d)
7-2	H	H	Ts	I	1	3	Syrup	1.31-1.49 (2H, m), 2.15-2.26 (2H, m), 2.44 (3H, s), 2.99 (2H, t), 3.54 (2H, d), 3.87 (1H, t), 7.05, 7.06, 7.64 (2H each, d), 7.20-7.35 (8H, m)
7-3	4-Cl	H	CHO	I	1	3	Syrup	1.46-1.63 (2H, m), 2.10-2.22 (2H, m), 3.10 (2H, t), 4.01 (2H, d), 5.08 (1H, br t), 7.06-7.39 (9H, m), 8.10 (1H, d)
7-4	4-MeO	H	CHO	I	1	3	Syrup	1.45-1.65 (2H, m), 2.09-2.22 (2H, m), 3.09 (2H, t), 3.80 (3H, s), 3.99 (2H, d), 5.00-5.15 (1H, br s), 6.80-6.90 (2H, m), 7.00-7.38 (7H, m), 8.10 (1H, d)
7-5	4-Cl	4-Cl	CHO	OTs	1	3	Syrup	1.30-1.60 (2H, m), 2.00-2.20 (2H, m), 2.45 (3H, s), 3.90-4.00 (4H, m), 5.00-5.20 (1H, br s), 7.00-7.40 (10H, m), 7.72 (2H, m), 8.08 (1H, d)
7-6	H	H	CHO	I	1	4	Syrup	1.07-1.28 (2H, m), 1.65-1.85 (2H, m), 2.00-2.13 (2H, m), 3.07 (2H, t), 4.04 (2H, d), 5.02 (1H, br s), 7.10-7.39 (10H, m), 8.10 (1H, d)
7-7	H	H	CHO	I	2	3	Syrup	1.43-1.61 (2H, m), 2.19-2.40 (4H, m), 3.08 (2H, q), 3.11 (2H, t), 5.19 (1H, br s), 7.12-7.36 (10H, m), 7.99 (1H, d)
7-8	H	H	Ts	I	2	3	Syrup	1.32-1.49 (2H, m), 2.02-2.17 (2H, m), 2.21-2.34 (2H, m), 2.42 (3H, s), 2.62-2.78 (2H, m), 3.05 (2H, t), 4.26 (1H, t), 7.06, 7.07, 7.61 (2H each, d), 7.12-7.32 (8H, m)
7-9	H	H	Ac	I	3	3	Syrup	1.12-1.28 (2H, m), 1.40-1.56 (2H, m), 1.91 (3H, s), 2.04-2.23 (4H, m), 3.10 (2H, t), 3.17 (2H, q), 5.25 (1H, br s), 7.11-7.32 (10H, m)

CLAIMS

What is claimed is

1. A composition for antagonizing MIP-1α/RANTES receptor comprising a compound of the formula:



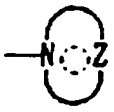
[I]

wherein Ar^1 and Ar^2 independently represent an optionally substituted aromatic group;

Q^1 and Q^2 independently represent an optionally substituted divalent C_{1-6} aliphatic hydrocarbon group which may have oxygen or sulfur within the carbon chain;

R^1 is a hydrogen atom, an optionally substituted lower alkyl group or an optionally substituted lower alkyl-carbonyl group;

R^2 is an optionally substituted hydrocarbon group or an acyl group, or R^1 and R^2, taken together with the adjacent nitrogen atom, may form an optionally substituted nitrogen-containing heterocyclic ring; and a group of the formula:



is an optionally substituted monocyclic or fused nitrogen-containing heterocyclic group, or a salt thereof.

2. A composition as claimed in claim 1, wherein

Ar^1 and Ar^2 independently represent (A) a monocyclic or fused polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms, or (B) a 5- to 11-membered monocyclic or fused heteroaromatic group having at least one of 1 or 2 kinds of h t ro atoms

select d from nitrogen, sulfur and oxyg n in addition to carbon atoms, said heterocyclic group being optionally fused with the monocyclic or fused polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms, each of which may have a substituent selected from the group consisting of

(1) a halogen atom,

(2) a C_{1-3} alkylenedioxy group,

(3) a nitro group,

(4) a cyano group,

(5) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(6) a C_{2-6} alkenyl group optionally having 1 to 3 halogen atoms,

(7) a C_{2-6} alkynyl group optionally having 1 to 3 halogen atoms,

(8) a C_{3-6} cycloalkyl group,

(9) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms,

(10) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms,

(11) a hydroxyl group,

(12) an amino group,

(13) a mono-C_{1-6} alkylamino group,

(14) a di-C_{1-6} alkylamino group,

(15) a 5- to 7-membered cyclic amino group,

(16) an acylamino group which is shown by (i) $-NHCOOR^3$, (ii) $-NHCONHR^3$, (iii) $-NHCOR^3$ or (iv) $-NHSO_2R^3$ wherein R^3 is (1) a C_{1-6} alkyl group, (2) a C_{2-6} alkenyl group, (3) a C_{2-6} alkynyl group, (4) a C_{3-6} cycloalkyl group which may be fused with a benzene ring optionally having 1 to 3 C_{1-6} alkoxy groups, (5) a C_{6-10} aryl group or (6) a C_{7-16} aralkyl group, each of a group shown by the above items (1) to (6) optionally having 1 to 5 substituents selected from th group consisting of

(a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro gr up, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(17) a C_{1-6} alkyl-carbonyl group,

(18) a carboxyl group,

(19) a C_{1-6} alkoxy-carbonyl group,

(20) a carbamoyl group,

(21) a mono-C_{1-6} alkyl-carbamoyl group,

(22) a di-C_{1-6} alkyl-carbamoyl group,

(23) a C_{6-10} aryl-carbamoyl group,

(24) a sulfo group,

(25) a C_{1-6} alkylsulfonyl group,

(26) a C_{6-10} aryl group, and

(27) a C_{6-10} aryloxy group;

Q^1 and Q^2 independently represent

(1) a C_{1-6} alkylene group,

(2) a C_{2-6} alkenylene group, or

(3) a C_{2-6} alkynylene group, each of a group shown by the above items (1) to (3) may have xyg n or

optionally oxydized sulfur within th carbon chain;

R^1 is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group which may have 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, or

(3) a C_{1-6} alkyl-carbonyl group which may have 1 to 5 substituents selected from (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carb xyl group, (o) a C_{1-6} alk xy-carbonyl group, (p) a

carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring;

R^2 is

(1) a C_{1-6} alkyl group,

(2) a C_{2-6} alkenyl group,

(3) a C_{2-6} alkynyl group,

(4) a C_{3-6} cycloalkyl group which may be fused with a benzene ring optionally having 1 to 3 C_{1-6} alkoxy groups,

(5) a C_{6-10} aryl group,

(6) a C_{7-16} aralkyl group,

each of a group shown by the above items (1) to (6) optionally having 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10}

aryloxy group and (x) a 5- to 7-membered h terocyclic group having 1 to 3 h tero atoms s lected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, or

(7) an acyl group which is shown by the formula: $-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$, $-(C=O)O-R^4$, $-(C=S)O-R^4$, or $-(C=S)NR^5R^4$, wherein R^4 is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group,

(iii) a C_{2-6} alkenyl group,

(iv) a C_{2-6} alkynyl group,

(v) a C_{3-6} cycloalkyl group which may be fused with a benzene ring optionally having 1 to 3 C_{1-6} alkoxy groups,

(vi) a C_{6-10} aryl group,

(vii) a C_{7-16} aralkyl group,

(viii) a 5- to 11-membered heterocyclic group having at least one hetero atom selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(ix) a C_{1-6} alkyl-carbonyl group,

(x) a carboxyl group,

(xi) a C_{1-6} alkoxy-carbonyl group,

(xii) a mono-C_{1-6} alkyl-carbamoyl group,

(xiii) a di-C_{1-6} alkyl-carbamoyl group,

(xiv) a 5- to 7-membered cyclic amino group, or

(xv) a C_{6-10} aryloxy group,

each of a group shown by the above items (ii) to (xv) optionally having 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally substituted with (e-1) a halogen atom, (e-2) a C_{1-3} alkylenedioxy

group, (e-3) a nitro group, (-4) a cyano group, (e-5) a C_{3-6} cycloalkyl group, (e-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (e-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (e-8) a hydroxyl group, (e-9) an amino group, (e-10) a mono-C_{1-6} alkylamino group, (e-11) a di-C_{1-6} alkylamino group, (e-12) a C_{1-6} alkyl-carbonyl group, (e-13) a carboxyl group, (e-14) a C_{1-6} alkoxy-carbonyl group, (e-15) a carbamoyl group, (e-16) a mono-C_{1-6} alkyl-carbamoyl group, (e-17) a di-C_{1-6} alkyl-carbamoyl group, (e-18) a C_{6-10} aryl-carbamoyl group, (e-19) a sulfo group, (e-20) a C_{1-6} alkylsulfonyl group, (e-21) a C_{6-10} aryl group, (e-22) a C_{6-10} aryloxy group or (e-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a C_{7-16} aralkyl group, (j) a hydroxyl group, (k) an amino group which may be substituted with a C_{1-6} alkyl carbonyl group, (l) a mono-C_{1-6} alkylamino group, (m) a di-C_{1-6} alkylamino group, (n) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (n-1) a halogen atom, (n-2) a C_{1-3} alkylenedioxy group, (n-3) a nitro group, (n-4) a cyano group, (n-5) a C_{3-6} cycloalkyl group, (n-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (n-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (n-8) a hydroxyl group, (n-9) an amino group, (n-10) a mono-C_{1-6} alkylamino group, (n-11) a di-C_{1-6} alkylamino group, (n-12) a C_{1-6} alkyl-carbonyl group, (n-13) a carboxyl group, (n-14) a C_{1-6} alkoxy-carbonyl group, (n-15) a carbamoyl group,

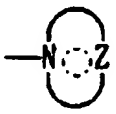
(n-16) a mono-C_{1-6} alkyl-carbamoyl group, (n-17) a di-C_{1-6} alkyl-carbamoyl group, (n-18) a C_{6-10} aryl-carbamoyl group, (n-19) a sulfo group, (n-20) a C_{1-6} alkylsulfonyl group, (n-21) a C_{6-10} aryl group, (n-22) a C_{6-10} aryloxy group or (n-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (o) a carboxyl group, (p) a C_{1-6} alkoxy-carbonyl group, (q) a formyl group which may be substituted with 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfure in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (r) a carbamoyl group, (s) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (s-1) a halogen atom, (s-2) a C_{1-3} alkylenedioxy group, (s-3) a nitro group, (s-4) a cyano group, (s-5) a C_{3-6} cycloalkyl group, (s-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (s-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (s-8) a hydroxyl group, (s-9) an amino group, (s-10) a mono-C_{1-6} alkylamino group, (s-11) a di-C_{1-6} alkylamino group, (s-12) a C_{1-6} alkyl-carbonyl group, (s-13) a carboxyl group, (s-14) a C_{1-6} alkoxy-carbonyl group, (s-15) a carbamoyl group, (s-16) a mono-C_{1-6} alkyl-carbamoyl group, (s-17) a di-C_{1-6} alkyl-carbamoyl group, (s-18) a C_{6-10} aryl-carbamoyl group, (s-19) a sulfo group, (s-20) a C_{1-6} alkylsulfonyl group, (s-21) a C_{6-10} aryl group, (s-22) a C_{6-10} aryloxy group or (s-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (t) a di-C_{1-6} alkyl-carbamoyl group whos alkyl portion may be

substituted with (t-1) a halogen atom, (t-2) a C_{1-3} alkyl nedioxy group, (t-3) a nitro group, (t-4) a cyano group, (t-5) a C_{3-6} cycloalkyl group, (t-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (t-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (t-8) a hydroxyl group, (t-9) an amino group, (t-10) a mono-C_{1-6} alkylamino group, (t-11) a di-C_{1-6} alkylamino group, (t-12) a C_{1-6} alkyl-carbonyl group, (t-13) a carboxyl group, (t-14) a C_{1-6} alkoxy-carbonyl group, (t-15) a carbamoyl group, (t-16) a mono-C_{1-6} alkyl-carbamoyl group, (t-17) a di-C_{1-6} alkyl-carbamoyl group, (t-18) a C_{6-10} aryl-carbamoyl group, (t-19) a sulfo group, (t-20) a C_{1-6} alkylsulfonyl group, (t-21) a C_{6-10} aryl group, (t-22) a C_{6-10} aryloxy group or (t-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (u) an optionally halogenated C_{6-10} aryl-carbamoyl group, (v) an optionally halogenated C_{6-10} aryl-carbonyl group, (w) a sulfo group which may be substituted with an amino group, (x) a C_{1-6} alkylsulfonyl group, (y) a C_{6-10} aryl group, (z) a C_{6-10} aryloxy group, (aa) a C_{2-6} alkenylamino group, (bb) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (cc) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (dd) a C_{1-6} alkoxy-carbamoyl group, (ee) a carbamoyloxy group, (ff) a sulfamoyl group, (gg) a mono-C_{1-6} alkyl-sulfamoyl group, and (hh) a di-C_{1-6} alkyl-sulfamoyl group;

R^5 is

1) a hydrogen atom r

2) a C_{1-6} alkyl group;
or R^1 and R^2, taken together with the adjacent nitrogen atom, form a 4- to 8-membered heterocyclic group optionally having at least one nitrogen and 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, which may have 1 to 5 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkoxy-carbonyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, and (w) a C_{6-10} aryloxy group;
a group of the formula:



is (1) a 4- to 9-membered monocyclic ring or (2) 6- to 14-membered bicyclic ring, each of which may have 1 or 2 unsaturated bonds and optionally having 1 or 2 substituents selected from the group consisting of
(i) a C_{1-6} alkyl group,
(ii) a C_{1-6} alkoxy group,
(iii) a C_{1-6} alkylthio group, each of a group shown by the above items (i) to (iii) may have 1 to 5

substituents selected from (a) a halogen atom, (b) a C_{1-3} alkylenedioxy group, (c) a nitro group, (d) a cyano group, (e) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, (f) a C_{3-6} cycloalkyl group, (g) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (h) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (i) a hydroxyl group, (j) an amino group, (k) a mono-C_{1-6} alkylamino group, (l) a di-C_{1-6} alkylamino group, (m) a C_{1-6} alkyl-carbonyl group, (n) a carboxyl group, (o) a C_{1-6} alkyl-carbamoyl group, (p) a carbamoyl group, (q) a mono-C_{1-6} alkyl-carbamoyl group, (r) a di-C_{1-6} alkyl-carbamoyl group, (s) a C_{6-10} aryl-carbamoyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group and (x) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,

(iv) a hydroxyl group,

(v) an amino group,

(vi) a mono-C_{1-6} alkylamino group,

(vii) a di-C_{1-6} alkylamino group,

(viii) a C_{1-6} alkyl-carbonyl group,

(ix) a carboxyl group,

(x) a C_{1-6} alkoxy-carbonyl group,

(xi) a carbamoyl group,

(xii) a mono-C_{1-6} alkyl-carbamoyl group,

(xiii) a di-C_{1-6} alkyl-carbamoyl group,

(xiv) a C_{6-10} aryl-carbamoyl group,

(xv) a sulfo group,

(xvi) a C_{1-6} alkylsulfonyl group,

(xv) a C_{6-10} aryl group, and

(xvi) a C_{6-10} aryloxy group.

3. A composition as claimed in Claim 1 wh rein R^1 is a hydrog n atom or a C_{1-6} alkyl group.

4. A composition as claimed in Claim 1 wherein R^1 is a hydrogen atom or methyl.

5. A composition as claimed in Claim 1 wherein R^1 is a hydrogen atom.

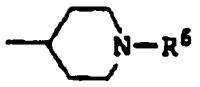
6. A composition as claimed in Claim 1 wherein R^7 is an acyl group.

7. A composition as claimed in Claim 6 wherein the acyl group is of the formula $-(C=O)-R^4$, $-SO_2-R^4$, $-SO-R^4$, $-(C=O)NR^5R^4$, $-(C=O)O-R^4$, $-(C=S)O-R^4$, or $-(C=S)NR^5R^4$, wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxy-carbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group, an optionally substituted 5- or 7-membered cyclic amino group or an optionally substituted aryloxy group; and R^5 is a hydrogen atom or a lower alkyl group.

8. A composition as claimed in Claim 6, wherein the acyl group is of the formula $-(C=O)-R^4$ or $-(C=O)NHR^4$, wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxy-carbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group, an optionally substituted 5- or 7-membered cyclic amino group or an optionally substituted aryloxy group; and R^5 is a hydrogen atom or a lower alkyl group.

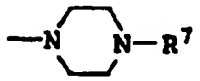
9. A compositi n as claimed in Claim 8, wherein R^4 is a group of the formula:

(1)



or

(2)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with
(b-1) a halogen atom, (b-2) a C_{1-3} alkylenedioxy group, (b-3) a nitro group, (b-4) a cyano group, (b-5) a C_{3-6} cycloalkyl group, (b-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (b-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (b-8) a hydroxyl group, (b-9) an amino group, (b-10) a mono-C_{1-6} alkylamino group, (b-11) a di-C_{1-6} alkylamino group, (b-12) a C_{1-6} alkyl-carbonyl group, (b-13) a carboxyl group, (b-14) a C_{1-6} alkoxy-carbonyl group, (b-15) a carbamoyl group, (b-16) a mono-C_{1-6} alkyl-carbamoyl group, (b-17) a di-C_{1-6} alkyl-carbamoyl group, (b-18) a C_{6-10} aryl-carbamoyl group, (b-19) a sulfo group, (b-20) a C_{1-6} alkylsulfonyl group, (b-21) a C_{6-10} aryl group, (b-22) a C_{6-10} aryloxy group or (b-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{3-6} cycloalkyl group, (d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (e) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (f) a C_{7-16} aralkyl group, (g) a hydroxyl group, (h) an amino

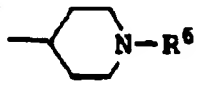
group, (i) a mono-C_{1-6} alkylamino group, (j) a di-C_{1-6} alkylamino group, (k) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (k-1) a halogen atom, (k-2) a C_{1-3} alkylenedioxy group, (k-3) a nitro group, (k-4) a cyano group, (k-5) a C_{3-6} cycloalkyl group, (k-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (k-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (k-8) a hydroxyl group, (k-9) an amino group, (k-10) a mono-C_{1-6} alkylamino group, (k-11) a di-C_{1-6} alkylamino group, (k-12) a C_{1-6} alkyl-carbonyl group, (k-13) a carboxyl group, (k-14) a C_{1-6} alkoxy-carbonyl group, (k-15) a carbamoyl group, (k-16) a mono-C_{1-6} alkyl-carbamoyl group, (k-17) a di-C_{1-6} alkyl-carbamoyl group, (k-18) a C_{6-10} aryl-carbamoyl group, (k-19) a sulfo group, (k-20) a C_{1-6} alkylsulfonyl group, or (k-21) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (l) a carboxyl group, (m) a C_{1-6} alkoxy-carbonyl group, (n) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (o) a carbamoyl group, (p) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (p-1) a halogen atom, (p-2) a C_{1-3} alkylenedioxy group, (p-3) a nitro group, (t-4) a cyano group, (p-5) a C_{3-6} cycloalkyl group, (p-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (p-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (p-8) a hydroxyl group, (p-9) an amino group, (p-10) a mono-C_{1-6} alkylamino group, (p-11) a di-C_{1-6} alkylamino group, (p-12) a C_{1-6} alkyl-carbonyl gr up,

(p-13) a carboxyl group, (p-14) a C_{1-6} alkoxy-carbonyl group, (p-15) a carbamoyl group, (p-16) a mono-C_{1-6} alkyl-carbamoyl group, (p-17) a di-C_{1-6} alkyl-carbamoyl group, (p-18) a C_{6-10} aryl-carbamoyl group, (p-19) a sulfo group, (p-20) a C_{1-6} alkylsulfonyl group, (p-21) a C_{6-10} aryl group, (p-22) a C_{6-10} aryloxy group or (p-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (q) a di-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (q-1) a halogen atom, (q-2) a C_{1-3} alkylenedioxy group, (q-3) a nitro group, (q-4) a cyano group, (q-5) a C_{3-6} cycloalkyl group, (q-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (q-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (q-8) a hydroxyl group, (q-9) an amino group, (q-10) a mono-C_{1-6} alkylamino group, (q-11) a di-C_{1-6} alkylamino group, (q-12) a C_{1-6} alkyl-carbonyl group, (q-13) a carboxyl group, (q-14) a C_{1-6} alkoxy-carbonyl group, (q-15) a carbamoyl group, (q-16) a mono-C_{1-6} alkyl-carbamoyl group, (q-17) a di-C_{1-6} alkyl-carbamoyl group, (q-18) a C_{6-10} aryl-carbamoyl group, (q-19) a sulfo group, (q-20) a C_{1-6} alkylsulfonyl group, (q-21) a C_{6-10} aryl group, (q-22) a C_{6-10} aryloxy group or (q-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (r) an optionally halogenated C_{6-10} aryl-carbamoyl group, (s) an optionally halogenated C_{6-10} aryl-carbonyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group, (x) a C_{2-6} alkenylamino group or (y) a 5- to 7-membered

heterocyclic group having 1 to 3 hetero atoms select d from nitr gen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring.

10. A composition as claimed in Claim 8, wherein R^4 is a group of the formula:

(1)



or

(2)

wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with

(b-1) a hydroxyl group, (b-2) a di-C_{1-6} alkylamino group, (b-3) a C_{1-6} alkoxy-carbonyl group, or (b-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{7-16} aralkyl group, (d) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (d-1) a halogen atom, (d-2) a mono-C_{1-6} alkylamino group, (d-3) a C_{1-6} alkoxy-carbonyl group, or (d-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (e) a C_{1-6} alkoxy-carbonyl group, (f) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said h terocyclic group b ing

optionally fused with benzene ring, (g) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (g-1) a halogen atom, or (g-2) a C_{1-6} alkyl-carbonyl group, (h) an optionally halogenated C_{6-10} aryl-carbamoyl group, (i) an optionally halogenated C_{6-10} aryl-carbonyl group, or (j) a C_{6-10} aryloxy group.

11. A composition as claimed in Claim 1 wherein Q^1 and Q^2 are independently a C_{1-6} alkylene group which may have an oxo group.

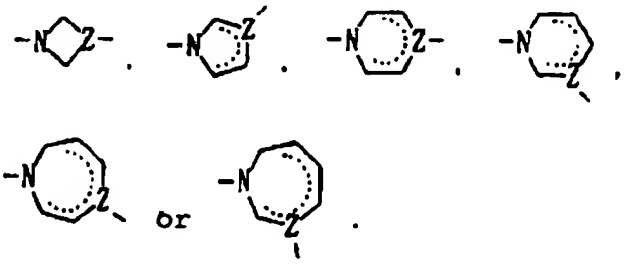
12. A composition as claimed in Claim 1 wherein Q^1 is a C_{1-4} alkylene group and Q^2 is a methylene group.

13. A composition as claimed in Claim 1 wherein the ring of the formula:

is a 4- to 9-membered monocyclic ring or 6- to 14-membered bicyclic ring, which may have 1 or 2 unsaturated bonds and may have 1 or 2 substituents in any position other than N and Z.

14. A composition as claimed in Claim 1 wherein the ring of the formula:

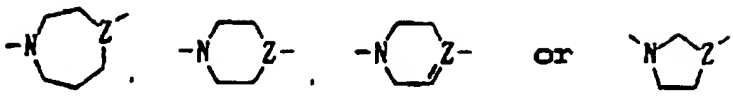
is



15. A composition as claimed in Claim 1 wh r in the

ring of the formula:

is



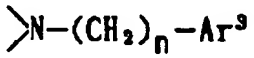
16. A composition as claimed in Claim 1 wherein the ring of the formula:

is

17. A composition as claimed in Claim 13 wherein Z is

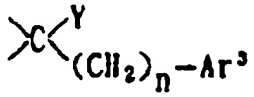
(1) an optionally substituted 1, 2-phenylene,

(2) a group of the formula:



wherein Ar^3 is an optionally substituted aromatic group, and n is an integer of 0 to 3,

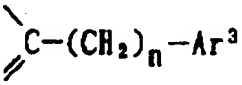
(3) a group of the formula:



wherein Ar^3 and n have the same meanings as defined above; and Y is (i) a hydrogen atom, (ii) an opti nally halogenated lower alkyl group, (iii) an

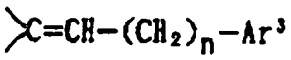
optionally halogenated low r alkoxy group, (iv) an optionally halogenat d lower alkylthio group, (v) a hydroxyl group, (vi) a cyano group, (vii) an alkyl-carbonyl group, (viii) a lower alkyl-carbonyloxy group, (ix) a formylamino group, (x) an amino group, (xi) a mono-lower alklylamino group, (xii) a di-lower alkylamino group, (xiii) a carboxyl group, (xiv) a lower alkoxy-carbonyl group or (xv) a lower alkyl-carbonylamino group, or

(4) a group of the formula:



wherein Ar^3 and n have the same meanings as defined above, or

(5) a group of the formula:

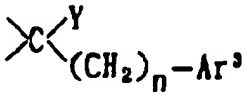


wherein Ar^3 and n have the same meanings as defined above.

18. A composition as claimed in Claim 1 wherein the ring of the formula:

is pyrrolidine, piperidine, piperazine, azepine or azocine, each of which may be fused with a benzene ring and may have a substituent.

19. A composition as claimed in Claim 13 wherein Z is a group of the formula:



wher in Ar^3 is an optionally substituted aromatic group, n is an int g r of 0 to 3, and Y is a hydrogen atom or a hydroxyl group.

20. A composition as claimed in Claim 19 wherein Ar^3 is a C_{6-14} aryl group or a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, each of which may have 1 to 3 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl group, and an optionally halogenated C_{1-6} alkoxy group.

21. A composition as claimed in Claim 19 wherein Ar^3 is a phenyl group optionally substituted with a halogen atom.

22. A composition as claimed in Claim 19 wherein n is 0.

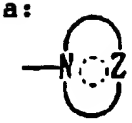
23. A composition as claimed in Claim 19 wherein Y is a hydroxyl group.

24. A composition as claimed in claim 1 wherein Ar^1 and Ar^2 independently represent a C_{6-14} aryl group or a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, each of which may have 1 to 3 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl group, and an optionally halogenated C_{1-6} alkoxy group.

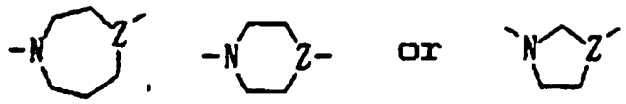
25. A composition as claimed in Claim 1 wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl.

26. A composition as claimed in claim 1, wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl; Q^1 is a C_{1-4} alkylene group; Q^2 is a methylene group;

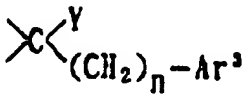
the group of th formula:



is



wherein Z is a group of the formula:



wherein Ar^3 is a phenyl group optionally substituted with a halogen atom, n is an integer of 0 to 3, and Y is a hydrogen atom or a hydroxyl group;
R^1 is a hydrogen atom or methyl;
R^2 is (1) an C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group or a formyl group or (2) an acyl group represented by the formula:
$-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)OR^4$
wherein R^4 is
(i) a hydrogen atom,
(ii) a C_{1-6} alkyl group which may have 1 to 5 substituents selected from (a) a hydroxyl group, (b) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (c) a mono-C_{1-6} alkylamino group, (d) a di-C_{1-6} alkylamino group, (e) a carboxyl group, (f) a C_{1-6} alkoxy-carbonyl group, (g) a mono-C_{1-6} alkyl-carbamoyl group, (h) a sulfo group which may be substituted with amino group, (i) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (j) a C_{1-6} alkoxy-carbamoyl group, and (k) a carbamoyloxy group,

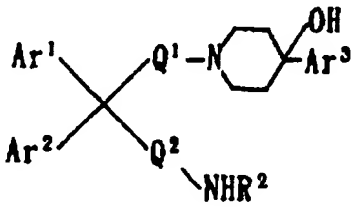
(iii) a C_{2-6} alkenyl group,
(iv) a C_{6-10} aryl group,
(v) a 5- to 11-membered heterocyclic group having at least one hetero atom selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,
(vi) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkyl-carbonyl group,
(vii) a carboxyl group which may be substituted with a C_{1-6} alkyl group,
(viii) a 5- to 7-membered cyclic amino group which may be substituted with
(a) a C_{1-6} alkyl group optionally substituted with (a-1) a hydroxyl group, (a-2) a di-C_{1-6} alkylamino group, (a-3) a C_{1-6} alkoxy-carbonyl group or (a-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,
(b) a C_{7-16} aralkyl group, (c) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (c-1) a halogen atom, (c-2) a mono-C_{1-6} alkylamino group, (c-3) a C_{1-6} alkoxy-carbonyl group or (c-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,
(d) a C_{1-6} alkoxy-carbonyl group, (e) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,
(f) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl

portion may b substituted with a halog n atom or a C_{1-6} alkyl-carbonyl group, (g) an optionally halogenated C_{6-10} aryl-carbamoyl group, (h) an optionally halogenated C_{6-10} aryl carbonyl group or (i) a C_{1-6} alkoxy-carbamoyl group, or

(ix) a C_{6-10} aryloxy group; and

R^5 is a hydrogen atom or a C_{1-6} alkyl group.

27. A compound of the formula:



[II]

wherein Ar^1, Ar^2 and Ar^3 independently represent an optionally substituted aromatic group;

Q^1 and Q^2 independently represent a divalent C_{1-6} aliphatic hydrocarbon group, which may have oxygen or sulfur within the carbon chain; and

R^2 is an optionally substituted hydrocarbon group or an acyl group or a salt thereof (except N-[5-[4-(4-chlorophenyl-4-hydroxypiperidino-2,2-diphenylpentyl]-1-methanesulfonamide hydrochloride, N-[5-[4-chlorophenyl)-4-hydroxypiperidino-2,2-diphenylpentyl]-1-(p-toluene)sulfonamide hydrochloride and N-[5-(4-(4-chlorophenyl)-4-hydroxypiperidino-2,2-diphenylpentyl]-1-(2-thiophene)sulfonamide hydrochloride).

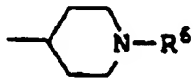
28. The compound of Claim 27 wherein R^2 is a group of the formula $-(C=O)-R^4$, $-(C=O)NR^5R^4$, $-(C=O)O-R^4$, $-(C=S)O-R^4$ or $-(C=S)NR^5R^4$ wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxylcarbonyl group, an optionally substituted

mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group or an optionally substituted 5- or 7-membered cyclic amino group; and R^5 is a hydrogen atom or a lower alkyl group.

29. A compound as claimed in Claim 27, wherein R^2 is the formula $-(C=O)-R^4$ or $-(C=O)NH-R^4$, wherein R^4 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxylcarbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group or an optionally substituted 5- or 7-membered cyclic amino group

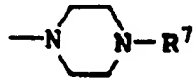
30. A compound as claimed in Claim 28, wherein R^4 is of the formula:

(1)



or

(2)



wherein R^6 and R^7 independently represent (a) a hydrogen atom, (b) a C_{1-6} alkyl group optionally substituted with

(b-1) a halogen atom, (b-2) a C_{1-3} alkylenedioxy group, (b-3) a nitro group, (b-4) a cyano group, (b-5) a C_{3-6} cycloalkyl group, (b-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (b-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (b-8) a hydroxyl group, (b-9) an amino group, (b-10) a mono-C_{1-6}

alkylamino group, (b-11) a di-C_{1-6} alkylamino group, (b-12) a C_{1-6} alkyl-carbonyl group, (b-13) a carboxyl group, (b-14) a C_{1-6} alkoxy-carbonyl group, (b-15) a carbamoyl group, (b-16) a mono-C_{1-6} alkyl-carbamoyl group, (b-17) a di-C_{1-6} alkyl-carbamoyl group, (b-18) a C_{6-10} aryl-carbamoyl group, (b-19) a sulfo group, (b-20) a C_{1-6} alkylsulfonyl group, (b-21) a C_{6-10} aryl group, (b-22) a C_{6-10} aryloxy group or (b-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (c) a C_{3-6} cycloalkyl group, (d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (e) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (f) a C_{7-16} aralkyl group, (g) a hydroxyl group, (h) an amino group, (i) a mono-C_{1-6} alkylamino group, (j) a di-C_{1-6} alkylamino group, (k) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (k-1) a halogen atom, (k-2) a C_{1-3} alkylenedioxy group, (k-3) a nitro group, (k-4) a cyano group, (k-5) a C_{3-6} cycloalkyl group, (k-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (k-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (k-8) a hydroxyl group, (k-9) an amino group, (k-10) a mono-C_{1-6} alkylamino group, (k-11) a di-C_{1-6} alkylamino group, (k-12) a C_{1-6} alkyl-carbonyl group, (k-13) a carboxyl group, (k-14) a C_{1-6} alkoxy-carbonyl group, (k-15) a carbamoyl group, (k-16) a mono-C_{1-6} alkyl-carbamoyl group, (k-17) a di-C_{1-6} alkyl-carbamoyl group, (k-18) a C_{6-10} aryl-carbamoyl group, (k-19) a sulfo group, (k-20) a C_{1-6} alkylsulfonyl group, or (k-21) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxyg n and sulfur in addition to carbon atoms, said

heterocyclic group being optionally fused with a benzene ring, (l) a carboxyl group, (m) a C_{1-6} alkoxy-carbonyl group, (n) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (o) a carbamoyl group, (p) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (p-1) a halogen atom, (p-2) a C_{1-3} alkylenedioxy group, (p-3) a nitro group, (t-4) a cyano group, (p-5) a C_{3-6} cycloalkyl group, (p-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (p-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (p-8) a hydroxyl group, (p-9) an amino group, (p-10) a mono-C_{1-6} alkylamino group, (p-11) a di-C_{1-6} alkylamino group, (p-12) a C_{1-6} alkyl-carbonyl group, (p-13) a carboxyl group, (p-14) a C_{1-6} alkoxy-carbonyl group, (p-15) a carbamoyl group, (p-16) a mono-C_{1-6} alkyl-carbamoyl group, (p-17) a di-C_{1-6} alkyl-carbamoyl group, (p-18) a C_{6-10} aryl-carbamoyl group, (p-19) a sulfo group, (p-20) a C_{1-6} alkylsulfonyl group, (p-21) a C_{6-10} aryl group, (p-22) a C_{6-10} aryloxy group or (p-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (q) a di-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with (q-1) a halogen atom, (q-2) a C_{1-3} alkylenedioxy group, (q-3) a nitro group, (q-4) a cyano group, (q-5) a C_{3-6} cycloalkyl group, (q-6) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, (q-7) a C_{1-6} alkylthio group optionally having 1 to 3 halogen atoms, (q-8) a hydroxyl group, (q-9) an amino group, (q-10) a mono-C_{1-6} alkylamino group, (q-11) a di-C_{1-6}

alkylamino group, (q-12) a C_{1-6} alkyl-carbonyl group, (q-13) a carboxyl group, (q-14) a C_{1-6} alkoxy-carbonyl group, (q-15) a carbamoyl group, (q-16) a mono-C_{1-6} alkyl-carbamoyl group, (q-17) a di-C_{1-6} alkyl-carbamoyl group, (q-18) a C_{6-10} aryl-carbamoyl group, (q-19) a sulfo group, (q-20) a C_{1-6} alkylsulfonyl group, (q-21) a C_{6-10} aryl group, (q-22) a C_{6-10} aryloxy group or (q-23) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring, (r) an optionally halogenated C_{6-10} aryl-carbamoyl group, (s) an optionally halogenated C_{6-10} aryl-carbonyl group, (t) a sulfo group, (u) a C_{1-6} alkylsulfonyl group, (v) a C_{6-10} aryl group, (w) a C_{6-10} aryloxy group, (x) a C_{2-6} alkenylamino group or (y) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring.

31. A compound as claimed in Claim 27 wherein Q^1 and Q^2 are independently a C_{1-6} alkylene group which may have an oxo group.

32. A compound as claimed in Claim 27 wherein Q^1 is a C_{1-4} alkylene group and Q^2 is a methylene group.

33. A compound as claimed in Claim 27 wherein Ar^3 is a phenyl group optionally substituted with a halogen atom.

34. A compound as claimed in claim 27 wherein Ar^1 and Ar^2 independently represent a C_{6-14} aryl group or a 5- to 7-membered heterocyclic groups having 1 to 3 hetero atoms of 1 or 2 kinds selected from nitrogen, oxygen and sulfur in addition to a carbon atom, each of which may have 1 to 3 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl group, and an

optionally halogenat d C_{1-6} alk xy group.

35. A compound as claimed in Claim 27 wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl.

36. A compound as claimed in claim 27, wherein Ar^1 and Ar^2 independently represent phenyl, 4-chlorophenyl, 4-fluorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl; Q^1 is a C_{1-4} alkylene group; Q^2 is a methylene group; R^2 is (1) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a C_{1-6} alkyl-carbonyl group or a formyl group or (2) an acyl group represented by the formula:

$-(C=O)-R^4$, $-SO_2-R^4$, $-(C=O)NR^5R^4$ or $-(C=O)O-R^4$

wherein R^4 is

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group which may have 1 to 5 substituents selected from (a) a hydroxyl group, (b) an amino group which may be substituted with a C_{1-6} alkyl-carbonyl group, (c) a mono-C_{1-6} alkylamino group, (d) a di-C_{1-6} alkylamino group, (e) a carboxyl group, (f) a C_{1-6} alkoxy-carbonyl group, (g) a mono-C_{1-6} alkyl-carbamoyl group, (h) a sulfo group which may be substituted with amino group (i) a 5- to 7-membered cyclic amino group which may have an oxo group or which may be substituted with a hydroxyl group, (j) a C_{1-6} alkoxy-carbamoyl group, and (k) a carbamoyloxy group.

(iii) a C_{2-6} alkenyl group,

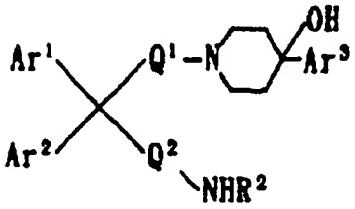
(iv) a C_{6-10} aryl group,

(v) a 5- to 11-membered heterocyclic group having at least one hetero atom selected from nitrogen, oxygen and sulfur in addition to a carbon atom, said heterocyclic group being optionally fused with a benzene ring,

(vi) a C_{1-6} alkyl group which may be substituted with a C_{1-6} alkyl-carbonyl gr up,

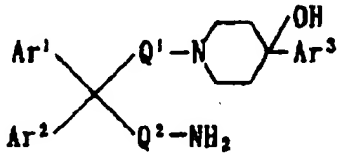
(vii) a carb xyl group which may be substituted with a C_{1-6} alkyl group,
(viii) a 5- to 7-membered cyclic amino group which may be substituted with
(a) a C_{1-6} alkyl group optionally substituted with (a-1) a hydroxyl group, (a-2) a di-C_{1-6} alkylamino group, (a-3) a C_{1-6} alkoxy-carbonyl group or (a-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(b) a C_{7-16} aralkyl group, (c) a C_{1-6} alkyl-carbonyl group whose alkyl portion may be substituted with (c-1) a halogen atom, (c-2) a mono-C_{1-6} alkylamino group, (c-3) a C_{1-6} alkoxy-carbonyl group or (c-4) a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(d) a C_{1-6} alkoxy-carbonyl group, (e) a formyl group which may be substituted with a 5- to 7-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur in addition to carbon atoms, said heterocyclic group being optionally fused with a benzene ring,
(f) a mono-C_{1-6} alkyl-carbamoyl group whose alkyl portion may be substituted with a halogen atom or a C_{1-6} alkyl-carbonyl group, (g) an optionally halogenated C_{6-10} aryl-carbamoyl group, (h) an optionally halogenated C_{6-10} aryl carbonyl group or (i) a C_{1-6} alkoxy-carbamoyl group, or
(ix) a C_{6-10} aryloxy group;
R^5 is a hydrogen atom or a C_{1-6} alkyl group; and
Ar^3 is a phenyl group optionally substituted with a halogen atom.

37. A process for producing a compound of th formula:



[II]

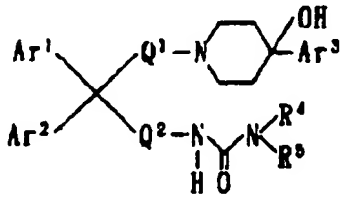
wherein R^2 is an acyl group, and the other symbols have the same meanings as defined in Claim 27 or a salt thereof, which comprises subjecting a compound of the formula:



(IX')

wherein the all symbols have the same meanings as defined in Claim 27 or a salt thereof to the acylation reaction.

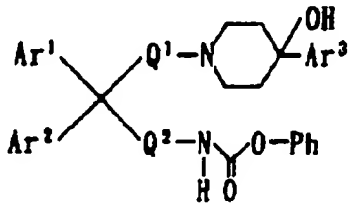
38. A process for producing a compound of the formula:



(II')

wherein R^4 represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted lower alkyl-carbonyl group, a carboxyl group, an optionally substituted lower alkoxy-carbonyl group, an optionally substituted mono-lower alkylaminocarbonyl group, an optionally substituted di-lower alkylaminocarbonyl group or an optionally

substituted 5- or 6-membered cyclic amino group; and R^6 is a hydrogen atom or a lower alkyl group, and the other symbols have the same meanings as defined in Claim 27 or a salt thereof, which comprises reacting a compound of the formula:



(X')

wherein Ph is a phenyl group, and the other symbols have the same meanings as defined above or a salt thereof with a compound of the formula:

[XI]

wherein R^4 and R^5 have the same meanings as defined above or a salt thereof.

39. A composition as claimed in Claim 1 which is a prophylactic or therapeutic agent for inflammatory diseases.

40. A composition as claimed in Claim 1 which is a prophylatic or therapeutic agent for allergic diseases.

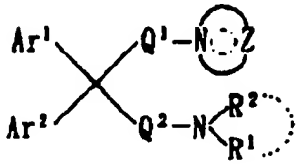
41. A composition as claimed in Claim 1 which is a prophylactic or therapeutic agent for arteriosclerosis, bronchial asthma, atopy, multiple sclerosis or rheumatoid arthritis.

42. A pharmaceutical composition comprising the compound of Claim 27.

43. A MIP-1α/RANTES receptor antagonist comprising the compound of claim 27.

44. A method of treating or preventing inflammatory diseases or allergic diseas s which comprises

administering to a mammal in need an effective amount of a compound of the formula:



[I]

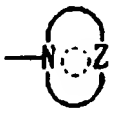
wherein Ar^1 and Ar^2 independently represent an optionally substituted aromatic group;

Q^1 and Q^2 independently represent an optionally substituted divalent C_{1-6} aliphatic hydrocarbon group which may have oxygen or sulfur within the carbon chain;

R^1 is a hydrogen atom, an optionally substituted lower alkyl group or an optionally substituted lower alkyl-carbonyl group;

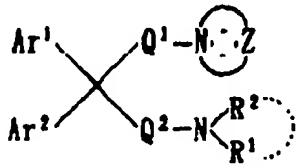
R^2 is an optionally substituted hydrocarbon group or an acyl group, or R^1 and R^2, taken together with the adjacent nitrogen atom, form an optionally substituted nitrogen-containing heterocyclic ring; and

a group of the formula:



is an optionally substituted monocyclic or fused nitrogen-containing heterocyclic ring, or a salt thereof.

45. Use of a compound of the formula:



[I]

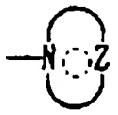
wherein Ar^1 and Ar^2 independently represent an optionally substituted aromatic group;

Q^1 and Q^2 independently represent an optionally substituted divalent C_{1-6} aliphatic hydrocarbon group which may have oxygen or sulfur within the carbon chain;

R^1 is a hydrogen atom, an optionally substituted lower alkyl group or an optionally substituted lower alkyl-carbonyl group;

R^2 is an optionally substituted hydrocarbon group or an acyl group, or R^1 and R^2, taken together with the adjacent nitrogen atom, form an optionally substituted nitrogen-containing heterocyclic ring; and

a group of the formula:



is an optionally substituted monocyclic or fused nitrogen-containing heterocyclic ring or a salt thereof, for the manufacture of a medicament for treating or preventing inflammatory diseases or allergic diseases.

46. A compound as claimed in claim 27, which is
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]-3-(piperidin-4-yl)urea,
Ethyl 4-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentylaminocarbonylamino] piperidino-4-oxobutyrate,
N-Ethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino-1-piperidinecarboxamide,
N-Ethoxycarbonylmethyl-4-[5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentyl]aminocarbonyl-amino-1-piperidinecarboxamide,
Ethyl 3-[4-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidino]-2,2-diphenylpentyl]aminocarbonylamino] piperidino-3-oxopropionate,
1-[5-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-

2,2-diph nylpentyl]-3-(1-ethylpiperidin-4-yl)urea,
1-[(Piperidin-4-yl)carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[(N-Ethylcarbamoyl)piperidin-4-yl]carboamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[N-(Ethoxycarbonylacetyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane,
1-[[N-(3-Methoxycarbonylpropionyl)piperidin-4-yl]carboxamido]-5-[4-(4-chlorophenyl)-4-hydroxypiperidino]-2,2-diphenylpentane, or a salt thereof.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/JP 96/03820

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/52 C07D295/12 C07D211/70 C07D401/04 C07D401/06
C07D401/12 C07D223/08 C07D409/06 C07D211/58 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	FR 2 408 599 A (DEVINTER SA) 8 June 1979 see the whole document	1-46
A	WO 94 11504 A (GENENTECH INC) 26 May 1994 see the whole document	1-46
A	WO 94 07521 A (UNIVERSITY OF TEXAS) 14 April 1994 see the whole document	1-46

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 1997	14.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kissler, B

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